Vol. 13 No. 1 March, 1954

ANNALS OF THE RHEUMATIC DISEASES

CONTENTS

LONDON
BRITISH MEDICAL ASSOCIATION
TAVISTOCK SQUARE, W.C.1

YEARLY SUBSCRIPTION (4 NUMBERS) TWO GUINEAS. U.S.A. $7.00. [illegible] 12s. 6d.

EDITORIAL

Observant readers of this journal will notice that the names of those responsible for its editorial direction which are printed on its front cover have changed. This is due to the retirement of Dr. C. W. Buckley from the editorial Chair which he has adorned from the foundation of the ANNALS until the beginning of this year.

Opportunity has been taken with the change to appoint one assistant editor and a small editorial committee, who will assist the new editor in his duties, together with an editorial board of experts who have kindly consented to act as assessors of all papers sent in for publication.

It is thought that in this way the high standard already achieved by the ANNALS will be maintained, and possibly in due course even improved.

This policy has the full agreement of our American editorial colleagues, who join with us in lamenting Dr. Buckley's decision to retire—whilst congratulating him on the approach of his eightieth birthday. This event will be the subject of further comment in a future issue.

W.S.C.C.

HEBERDEN ORATION, 1953

SPONDYLOSIS : THE KNOWN AND THE UNKNOWN

BY

SIR RUSSELL BRAIN

President of the Royal College of Physicians

This Society has always concerned itself with the broad social effects of disease, and degeneration of the intervertebral disks is responsible for a very large amount of pain, suffering, and disability, ranging from episodes which, however painful, are comparatively short-lived though they may be recurrent, to permanent incapacity of the most severe and disabling kind. Moreover, intervertebral disk degeneration is, on the whole, a disorder of the second half of life, occurring particularly in the 5th and 6th decades; hence, as we have an ageing population, the condition is steadily increasing in frequency and in social importance.

My interest in the subject has been primarily concerned with the effects of the disk degeneration upon the nervous system, but the neurological manifestations are, of course, end-results, which often only declare themselves after the disk lesion has been present for many years; so if we are to prevent these most disabling consequences of disk degeneration we must learn far more than we know at present about their aetiology. For, even when the disk degeneration has already occurred and has brought the patient to the doctor on account of pain in the spine or damage to the nerve roots or the spinal cord, we still know far too little about what is really happening, and often have insufficient knowledge upon which to base a rational therapy. Our problem, then, is to correlate the patient's symptoms and signs with the radiological appearance of the affected portion of the spine, and both with the pathological changes responsible for the symptoms. For example, the patient's symptoms may be acute and severe, yet it may be difficult to detect any radiological abnormality. At the other extreme we see patients with gross radiological changes but no symptoms at all. In between fall those patients who seem at first sight the easiest to understand, namely, those who have chronic symptoms associated with chronic changes as shown by the *x* rays, but it is equally likely that another patient with *x* rays which show apparently similar chronic changes will come to the doctor on account of symptoms which are acute. These discrepancies, which could easily be multiplied, show how difficult it is in many cases to form an opinion as to the precise nature of the pathological change responsible for the current symptoms; without that knowledge, treatment must be, as we must admit it often is, largely empirical. Hence the differing views about the value of, and indications for, physiotherapy of various kinds, immobilization, traction, manipulation, and operation.

Nomenclature in Relation to Pathology

I do not propose to deal with those lesions of the intervertebral disks which are produced by their invasion by neoplasms or by infection: I shall confine myself to the changes which have come to be grouped under the term "spondylosis", which, of course, implies that the lesions are degenerative and not inflammatory. This term, however, is itself deceptively simple, if it is taken to mean that we are dealing with a single pathological process: current terminology reflects the confusion in our ideas about the pathogenesis of what is called spondylosis. Sometimes the term "herniation" of the intervertebral disks is used, and sometimes the term "protrusion"; and it is widely believed that the two are synonymous. Frykholm (1951b) points out that

> the large amount of data available concerning the thoraco-lumbar disks cannot, however, be used indiscriminately to explain the pathologic condition affecting the cervical disks. The two groups differ too much both anatomically and with regard to the forces to which they are subjected. This is also apparent from the fact that in the cervical region soft nuclear herniations, similar to those in the lumbo-sacral region, are relatively infrequent compared to the hard and calcified types.

Nevertheless, I believe that the pathological classification of cervical disk protrusions which Frykholm has himself proposed is equally applicable to intervertebral disk protrusions occurring lower in the spine, provided suitable qualifications as to their pathogenesis are introduced.

In 1948 I suggested (Brain, 1948) a distinction between two main types of intervertebral disk protrusion: nuclear herniations and annular protrusions; and this distinction has been confirmed by Frykholm.

(1) *Nuclear herniation* probably starts with swelling of the nucleus. The annulus, which is encroached upon by the expanding nucleus, undergoes fibrillary degeneration. Its inner fibres merge with the nucleus while its outer fibres disintegrate, as the result of which nuclear material may be extruded into one or other intervertebral foramen, or more dorsally. Bull (1948) has calculated that the total volume of the nucleus pulposus in the cervical region corresponds to that of a red currant. Theoretically, therefore, this would be the maximal size of a complete nuclear herniation. Frykholm points out, however, that the mass always contains fragments of the annulus, and it has, in addition, a tendency to grow in size through a process of metaplasia and the addition of new tissue. The nuclear material is replaced by fibrous and cartilaginous elements and may show evidence of inflammatory reaction. Calcification or ossification may supervene. The mass finally presents the appearance of a well-defined tumour.

(2) *Annular protrusion* is produced by a different process. Owing to various factors, of which age is probably the most important, the intervertebral disk becomes dehydrated and loses its elasticity. As a result it collapses and the annulus bulges in all directions. Local bulgings may also occur at some point if the fibres of the annulus are less resistant. The protruded material becomes vascularized and its fibrous elements are increased in the same manner as in the nuclear herniation. Similarly, the added tissue increases the size of the original protrusion, and again calcification or ossification may occur.

So far we have been describing the alterations which occur in the intervertebral disks themselves, but the impairment of their normal functions leads to reactive changes in the bodies of the adjacent vertebrae. These are stimulated to new bone formation, *i.e.* to the production of the osteophytes which tend to fuse with the disk protrusions (Fig. 1). Frykholm distinguishes two types of osteophytes: the one which is produced in the manner just described he calls marginal lipping, which may either be localized or affect the entire circumference of the vertebral margins. Ventral spurs, on the other hand, are anatomically related to the anterior longitudinal

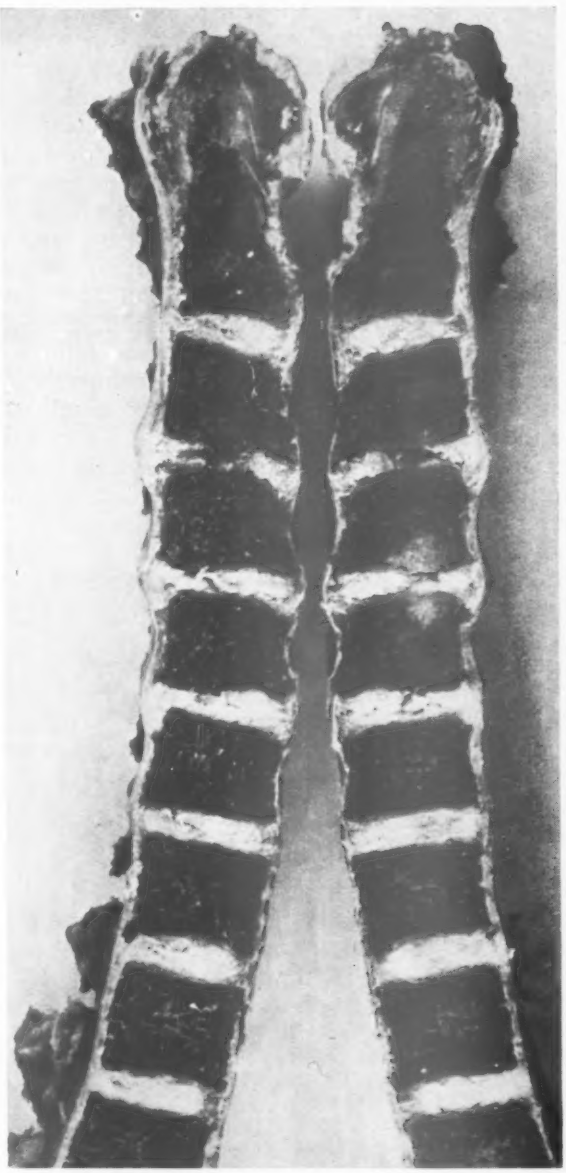


Fig. 1.—Sagittal section of cervical spine showing intervertebral disk degeneration and formation of posterior osteophytes. (Kindly lent by Dr. M. I. P. Wilkinson.)

ligaments and, according to Schmorl (1929), result from increased strain on this ligament, the fibres of which are firmly attached to the vertebral margins. Furthermore, the collapse of a disk also results in subluxation of the corresponding intervertebral joints with secondary osteophyte formation on the articular processes, leading to further narrowing of the intervertebral foramina.

If, as I believe, this account is fundamentally correct, it follows that "intervertebral disk pro-

trusion" is a name applied to two conditions pathologically distinct: one type of protrusion is the product of a nuclear herniation, while the other is not a herniation but an annular protrusion. A nuclear herniation which has occurred acutely and which is observed before it has had time to harden may be relatively soft; later calcification and ossification, together with the reactive bony changes in the adjacent vertebrae, may make it extremely difficult to distinguish from an annular protrusion which has resulted from disk degeneration. But the matter is more complicated than that, because the beginnings of a nuclear protrusion, which goes no further than to tear some of the fibres of the annulus, may interfere with the function of the intervertebral disk in the same way as primary degeneration, and may excite the same reactions from adjacent vertebrae, so that the changes which tend to produce nuclear protrusion are probably one cause of disk degeneration. Finally, be it noted, intervertebral disk degeneration may occur without causing protrusion.

Thus, when we use the term spondylosis, we are describing processes which are not pathologically homogeneous; we are dealing with a spine which manifests the end-results of either or both of two distinct pathological processes, nuclear herniation and annular protrusion. To some extent radiography is responsible for suggesting that spondylosis is a single disorder, since in the late stages it is not, as far as I know, possible to distinguish the one type from the other by means of *x* rays. If we are to study the natural history of what is called spondylosis, however, we cannot confine ourselves to the end-results, but must also take into account the acute nuclear herniation with which one type of spondylosis begins.

Problems of Aetiology

We see, therefore, how complex the causation of spondylosis may be. How large a part does trauma play? In our series of cases of cervical spondylosis (Brain, Northfield, and Wilkinson, 1952), two-thirds of our patients gave no history of trauma, and only six out of 45 gave a history of trauma which could possibly have contributed to the causation of the disorder. Nevertheless, the frequency with which disk degeneration is limited to a single disk (*e.g.* in eighteen out of 38 of our cases of cervical spondylosis), and the fact that it is very common in the lumbar spine, suggest that local causes are at least as important as a diffuse degenerative process, and that a minor trauma which may have started the process years previously may easily have been forgotten. The role of trauma in producing acute disk protrusion in the lumbar region is well recognized, and it may often exacerbate a pre-existing one.

The wear and tear of normal spinal movements may be a contributory factor, especially when disk degeneration has already begun; and congenital abnormalities, especially Klippel-Feil fusion, throw an added strain on adjacent articulations. Undoubtedly the most important causal factor is the biochemical change in the intervertebral disks which occurs with ageing and is associated with loss of water (Collins, 1949). The nature of this change has been studied by Sylvén, Paulson, Hirsch, and Snellman (1951): by means of electron microscopy they have shown that the healthy nucleus pulposus consists of an intercellular matrix, a three-dimensional lattice gel system containing a dense network of poorly differentiated collagenous fibrils and an amorphous interfibrillar substance. In the process of ageing this substance exhibits an irregular disappearance of the amorphous mucoid material which is responsible for the high water-content and water-binding capacity of the tissue. As a result there is a loss of turgescence and diminution in the vertical height of the disk, and this desiccation renders the spinal column more susceptible to both major and minor injuries.

Pathology of the Nerve Roots in Cervical Spondylosis

We owe much of our knowledge of the structure of the coverings of the nerve roots of the cervical spine, and their relationship to the cervical vertebrae, to the careful studies of Frykholm (1951c). The cervical intervertebral foramina are bounded above and below by the pedicles of the two adjacent vertebrae. The radicular nerves are situated in the foramina, and the dorsal root ganglia lie just outside in the gutter of the transverse process. The posterior wall of the foramen is formed by the superior articular process of the vertebra below, which, in turn, is covered posteriorly by the inferior articular process of the vertebra above. The ventral delimitation of the foramen is effected partly by the two adjacent vertebral bodies and partly by the dorsolateral rim of the intervertebral disk. This is termed the uncinate process, and there has been some discussion whether between the uncinate process of the lower vertebra and the corresponding facet of the vertebra above there is a true joint, as Luschka (1858) supposed. This has been called the uncovertebral joint and the neurocentral joint, but some, including Frykholm (1951b), believe that what has been regarded as a joint cavity is merely part of the annulus of the intervertebral disk.

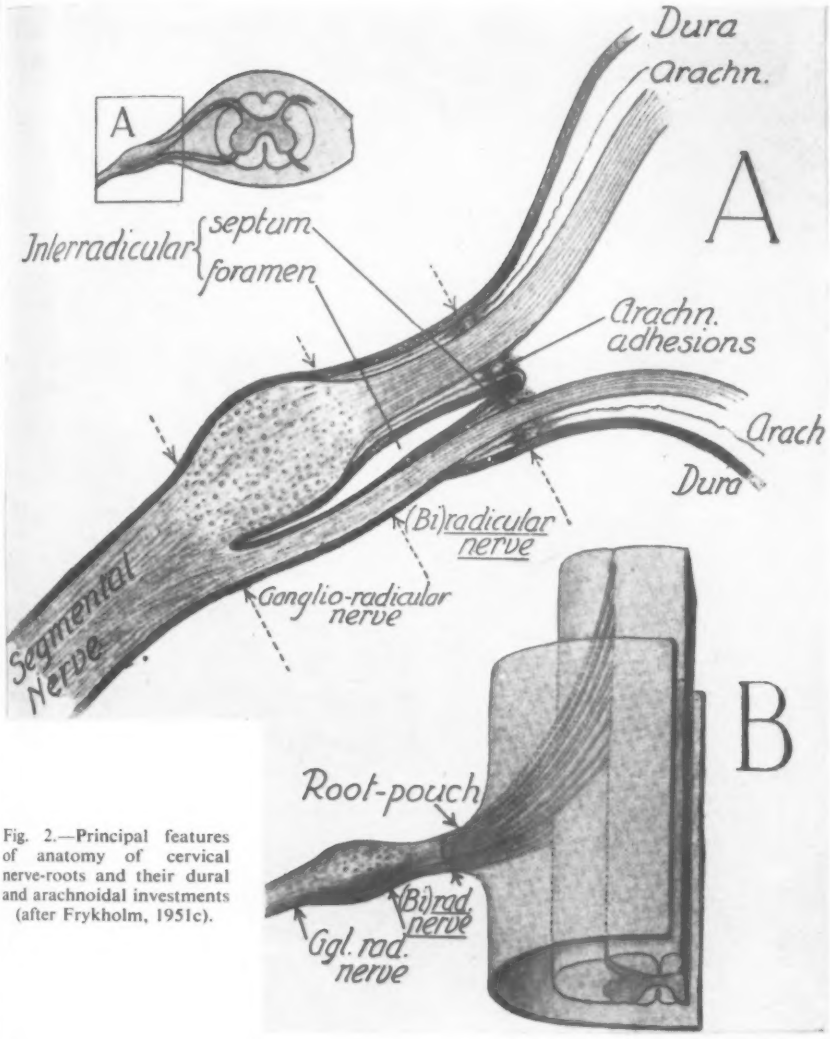


Fig. 2.—Principal features of anatomy of cervical nerve-roots and their dural and arachnoidal investments (after Frykholm, 1951c).

The rather complicated structure of the investment of the radicular nerves can be best understood by reference to a diagram (Fig. 2). Opposite each foramen the dural sac has a small infundibular extension, the dural root-pouch, or axillary pouch of some authors. By means of the funnel-like shape of the pouches, each nerve-root is conveyed in a smoothly curved course to the point at which it leaves the dural sac. At the bottom of the root-pouches are two openings, the dural root ostia, one ventral and one dorsal, which are separated by a small dural septum, the inter-radicular septum. Each root ostium leads into an individual root sleeve, of which there are consequently two, one dorsal and one ventral. The root sleeves, which are lateral extensions of the dural sacs, are separated by a small cleft known as the inter-radicular foramen. Consequently, outside the dural sac, the dorsal and ventral roots pass through individual sheaths which are entirely separated. A tubular extension of the arachnoid membrane encloses each root in its proper root-sleeve. Between the dural sac and the dorsal root ganglion the two roots lie close together and form an anatomical entity referred to as the radicular nerve.

In seeking to interpret the effect of the bony changes of cervical spondylosis upon the radicular nerves, it is of cardinal importance to remember that the radicular nerve normally occupies only one-fifth to one-fourth of the diameter of the foramen, hence if the nerve lay always in the middle considerable narrowing of the foramen could occur without producing any effect upon it. Frykholm (1951c), however, pointed out that the morphology of the lower cervical radicular nerves and their root-pouches is very variable (Fig. 3, overleaf). In early childhood the dural sac and the radicular nerves are only loosely attached to the bone. As age advances they gradually become relatively well fixed in their definite positions. In most cases the radicular nerves then take a slightly downward course and pass through the centre of their respective foramina. Variations in this arrangement may occur in normal individuals, probably as the result of disproportionate growth of the dural sac and the cord relative to the vertebral column. Displacement of the radicular nerves within the foramina may, however, occur also as the result of cervical disk degeneration, quite independently of the pressure of disk protrusion, since the cord and the dural sac retain their original length while the spine is shortened owing to osteoporosis and disk degeneration. The lower cervical radicular nerves thus tend to be displaced

Fig. 3.—Dissection of cervical nerve-roots in their passage through the intervertebral foramina, showing variations in shape of the dural root-pouches (Dr. R. J. Harrison).

towards the lower part of their foramina and hence become more upwardly directed. The displacement downwards also tends to distort the root-pouches, which results in sharp angulation of the nerve roots, and at this point of angulation the roots are subjected to undue strain and increased friction with the dural lining. Frykholm points out that in

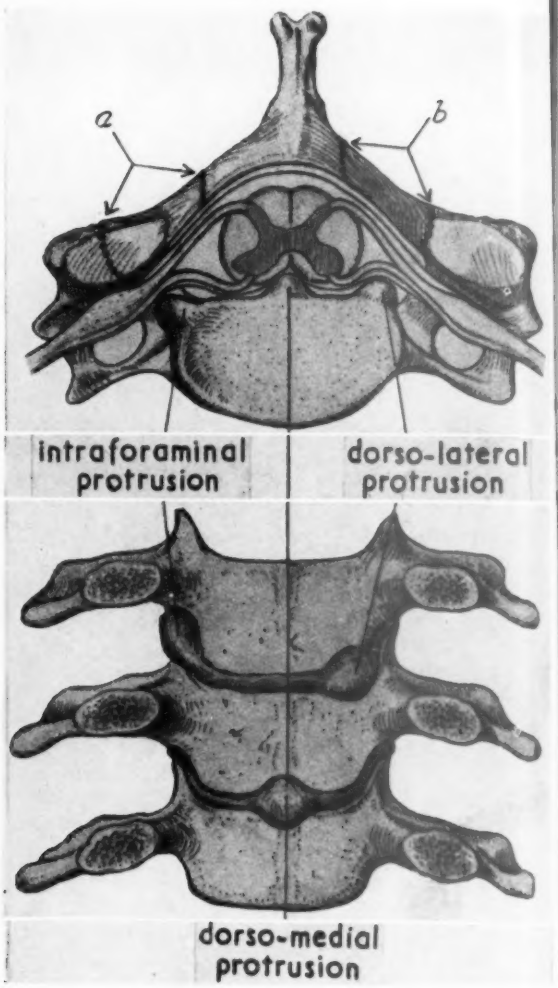


Fig. 4.—Principal types of disk protrusion (after Frykholm, 1951b).
(*i*) dorso-medial, producing bilateral cord compression.
(*ii*) dorso-lateral, producing radicular compression intraspinally.
(*iii*) intraforaminal, producing radicular compression with the intervertebral foramen.

consequence the segmental level of such a lesion does not necessarily correspond to a level of a disk degeneration.

Now let us consider the more direct effect of cervical intervertebral disk protrusion and the associated vertebral changes upon the nerve roots and radicular nerves. In this connexion I shall not concern myself with acute nuclear herniation, but with the end-results of disk protrusion, however produced, and disk degeneration in cervical spondylosis. Such disk protrusions have been variously classified according to their position in the circumference of the disk (Figs 4 and 5). One or more of these different types of protrusion may be encountered in the same disk, and they merge into one another. From the

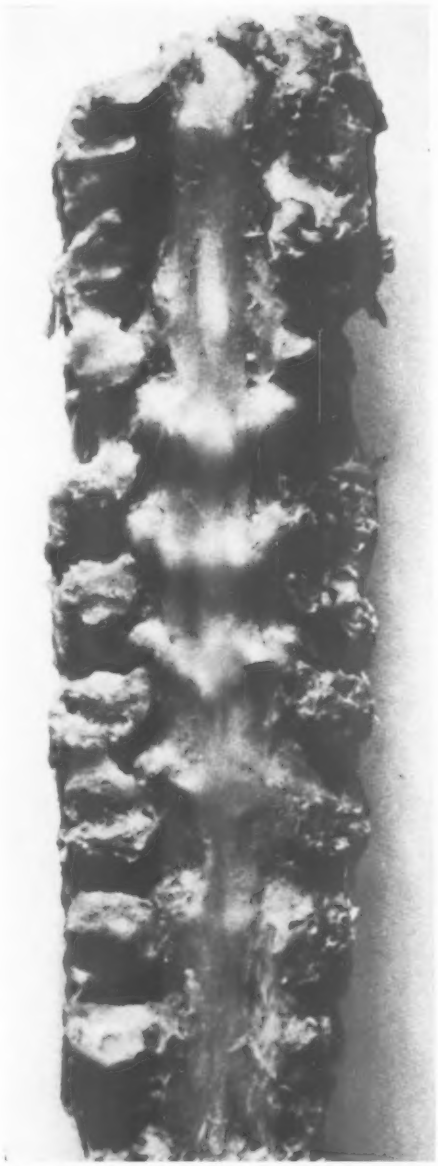


Fig. 5.—Posterior aspect of bodies of cervical vertebrae in spondylosis, showing central, dorso-lateral, and foraminal osteophytes. (Kindly lent by Dr. M. I. P. Wilkinson.)

point of view of the radicular nerves and nerve-roots, however, the only two with which we need concern ourselves are the dorsolateral protrusion, which does not invade the intervertebral foramen but may compress the intrameningeal nerve roots against the vertebral laminae, and the intraforaminal protrusion, which emerges from the uncinate part of the disk and compresses the radicular nerve against the articular processes. The mechanism of root compression, however, depends, not only upon the size and location of the protrusion, but also upon the angulation of the radicular nerve and its situation in the foramen. Thus, for example, a protrusion restricted to the lower part of the foramen may leave the roots quite intact if the radicular nerve is downwardly directed and situated cranially in the foramen, whereas, if the nerve is caudally situated and outwardly or upwardly directed, there is a much greater chance that it will be implicated. Furthermore, a protrusion which is strictly localized to the lower half of the foramen may produce a selective compression of the ventral root and leave the dorsal root intact, because the ventral root often runs along the caudal border of the dorsal root. Finally, cervical disk degeneration without protrusion may lead to marginal lipping as a result of the increased stress, which falls directly upon the vertebrae when the disk loses its shock-absorbing properties. This may cause some osteophyte formation in the anteromedial part of the intervertebral foramen. At the same time the narrowing of the disk throws an additional strain upon the corresponding intervertebral joints and that leads to secondary osteophyte formation on the articular processes, thus narrowing the foramen posterolaterally.

The pathological effects of these bony changes in the neighbourhood of the intervertebral foramen have been studied by Frykholm (1951a). In their fully developed form they consist of what he calls "root-sleeve fibrosis". This is characterized by:

(1) thickening and opacity of the dural root-sleeve and adjacent parts of the dural sac (*i.e.* the root pouch);

(2) narrowing, or complete abolition, of the dural funnel which forms the root pouch;

(3) sharpening of the upper and lower duroradicular junctions, which sometimes causes a distinct constriction or notching of the radicular nerve;

(4) thickening of the dura at the root-ostia and occasionally, also, thickening of the inter-radicular septum, resulting in a constricting ring of fibrous tissue around each nerve root;

(5) thickening and fibrosis of the arachnoid membrane in the neighbourhood of the root-ostia;

(6) disintegration and hyalinization of the dural tissue involved.

The chronic constriction of the nerve-roots and radicular nerve and the associated ischaemia leads in time to the degeneration of the nerve fibres. Frykholm points out that in many cases root-sleeve fibrosis is observed in the absence of any constriction of the corresponding foramen, though in such cases there is usually radiological evidence of disk degeneration, either at the same segmental level or at one or two levels above that of the radicular lesion. Occasionally also root-sleeve fibrosis may be present, in spite of the fact that *x* ray of the cervical spine shows no abnormality.

Thus, cervical intervertebral disk degeneration initiates a complex and variable series of changes which may affect the nerve roots and radicular nerve in many different ways needing individual assessment in each case. These changes may be summarized as follows:

(1) Disk degeneration affects the mobility of the cervical spine. The simplest example of this is the effect of degeneration of a single disk. Usually this greatly limits flexion and extension at the intervertebral joints between the two vertebrae separated by the affected disk, since the main movements must now occur above and below, and abnormal stresses may fall not only upon adjacent intervertebral joints but also upon adjacent radicular nerves. Exceptionally, disk degeneration leads to abnormal mobility, in which case, as a rule, the body of the upper vertebra slips forward upon that of the lower on flexion and slips back again on extension, a movement which must obviously tend to produce damage to the radicular nerves in the corresponding foramina.

(2) Narrowing of intervertebral disks shortens the cervical spine and disturbs the relationship between the radicular nerves and their corresponding foramina, the lower ones, particularly, tending to rest upon the lower margins of the foramina and to be kinked over them.

(3) Disk degeneration by itself can produce lipping of the adjacent vertebral bodies and so narrow the inner margins of the intervertebral foramina, whilst increased strain upon the intervertebral articulations produces osteophytic narrowing posteriorly.

(4) All this may occur without intervertebral disk protrusion. In addition, however, a dorsolateral protrusion may compress the nerve roots within the spinal canal, while an intraforaminal protrusion may compress them or the radicular nerve within the foramen.

(5) All the above-mentioned processes tend to lead to root-sleeve fibrosis, the characteristic reaction of the investment of the nerve roots and radicular nerve to chronic irritation and compression. These pathological changes, therefore, though most likely to occur in the nerve roots which pass through the intervertebral foramina at the level of the degenerated disk, may be present also at other levels at which there is no evidence of disk degeneration.

(6) The affected nerve-roots and radicular nerves, tethered to the foramina by root-sleeve fibrosis and lacking their normal mobility, are far more susceptible to trauma than the normal nervous tissue.

Consequently, not only may severe and lasting radicular symptoms be set up by head injury in such cases, but it is probable that comparatively slight trauma may be responsible for the acute onset of symptoms in patients with cervical spondylosis, symptoms which may be multiradicular in distribution although the bony pathological changes may be limited to one intervertebral disk and its adjacent vertebrae.

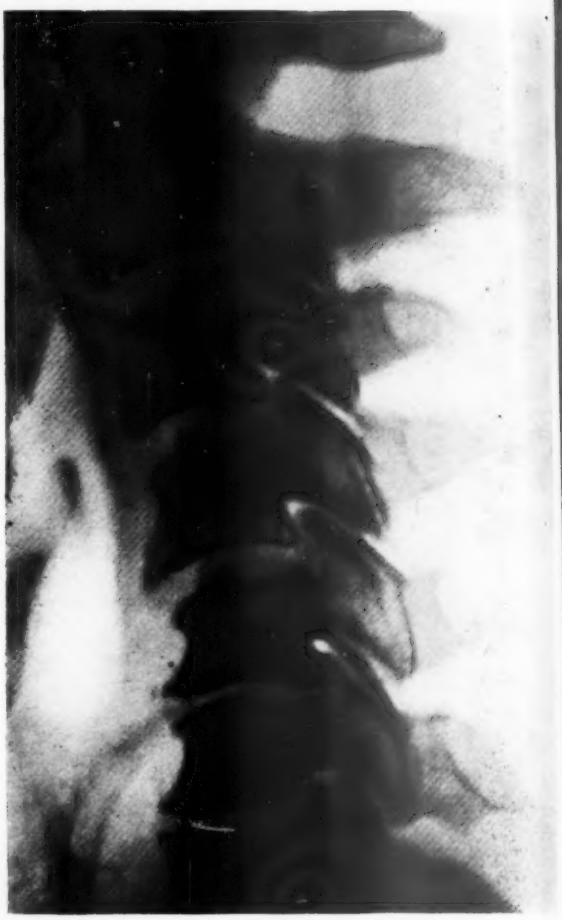


Fig. 6.—Cervical spine, showing results of spondylosis:
(*i*) narrowing of C5-6 and C6-7 disk-spaces with anterior and posterior osteophytes,
(*ii*) spondylolisthesis, C4 slipping forward on C5 in flexion.

Significance and Insignificance of Radiographic Changes

We are now in a position to assess the value and limitations of radiography in the diagnosis of the radicular lesions accompanying cervical spondylosis, and also, perhaps, to clear up some of the apparent anomalies. In the radiological investigation of a patient suspected of cervical spondylosis, it is usually necessary to take three lateral views in the erect, flexed, and extended positions respectively, as well as an antero-posterior view and right and left oblique views to show the intervertebral foramina. Without the flexed and extended lateral views it may be impossible to detect spondylolisthesis (Fig. 6).

In addition, plain *x* rays may show a narrowed intervertebral disk space, indicating disk degeneration; posterior osteophytes, in the manifestation of which specially soft films may be helpful; and osteo-

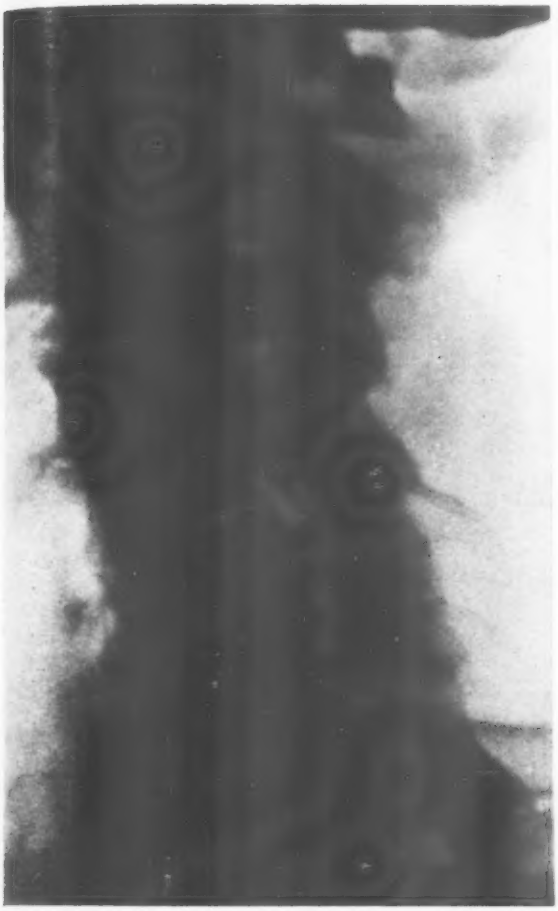


Fig. 7.—Oblique view, showing narrowing of intervertebral foramina C5-6 and C6-7 by osteophytes.

Fig. 8.—Myelogram, showing compression of the spinal cord by disk protrusions C3-4 and C5-6. Note slightness of narrowing of disks anteriorly and absence of anterior osteophytes.

phytic invasion of the intervertebral foramina (Fig. 7).

It is important to bear in mind the following points in the interpretation of the radiological appearances:

(1) A narrowed intervertebral disk space indicates disk degeneration which may or may not be associated with disk protrusion.

(2) The absence of posterior osteophytes, which are radiographically visible, does not necessarily mean the absence of a disk protrusion.

(3) A normal intervertebral foramen does not necessarily mean healthy nerve-roots or radicular nerves, since

(4) The nerve-roots may be compressed in the spinal canal by a dorso-lateral disk protrusion, which does not involve the foramen, or they may be the subject of root-sleeve fibrosis within a normal foramen for one of the reasons mentioned above.

(5) A narrowed intervertebral foramen does not necessarily mean that the corresponding nerve roots or radicular nerves are compressed, since normally the nerve takes up only a small proportion of the space in the foramen and if it is centrally situated may for a long time avoid damage or even tolerate a considerable degree of compression without giving rise to symptoms.

(6) Myelography may be valuable for the purpose of showing a disk protrusion, which is not visible in the plain *x* rays (Fig. 8), or a root-sleeve fibrosis, which may be demonstrable by obliteration of the root pouch in the myelogram although the intervertebral foramen may appear normal in plain *x* rays (Fig. 9, overleaf).

Some Radicular Syndromes of Cervical Spondylosis

I believe that the various clinical pictures described in the past as "brachial neuritis" or "brachial neuralgia" are in most cases caused by the pathological changes described by Frykholm as root-

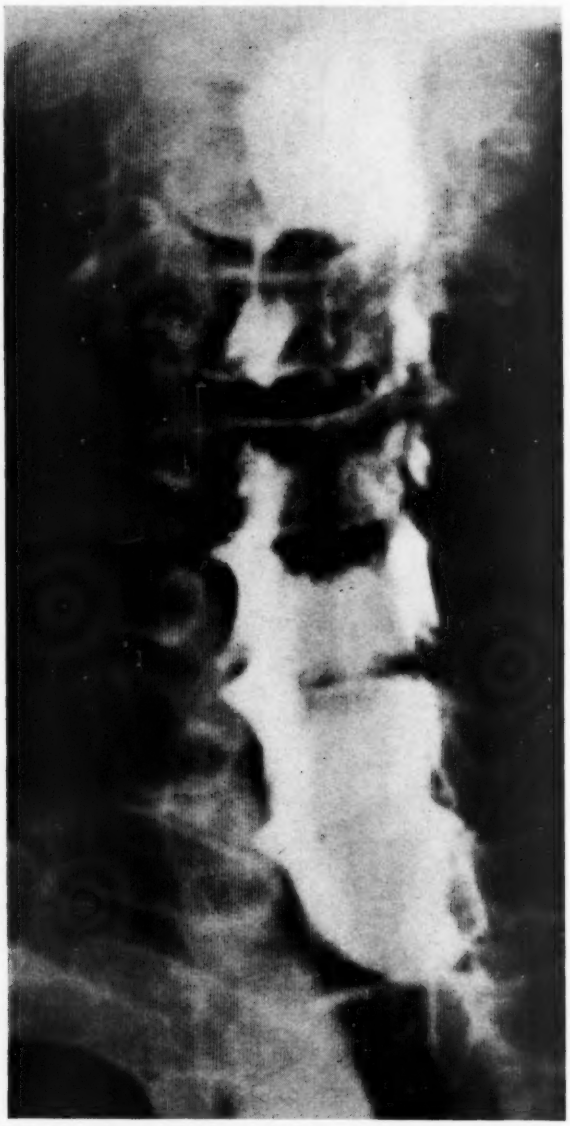


Fig. 9.—Antero-posterior myelogram in cervical spondylosis, showing filling defects caused by disk protrusions. Note particularly defective filling of root sheaths.

sleeve fibrosis. I shall not now retread the well-worn path of the clinical symptomatology of "brachial neuritis", but shall confine myself to a consideration of some of the less familiar clinical pictures and, in particular, those upon which light is thrown by the newer knowledge of the pathology of the condition.

(1) *Acroparaesthesiae.*—These may be defined as unpleasant tingling sensations affecting some or all of the digits of one or both upper limbs, developing during the night and usually passing off within an hour or so of awakening, which are particularly liable to occur in middle-aged women. Thus defined, they are merely symptomatic, and it is inherently unlikely that a symptom of irritation of sensory nerve fibres is characteristic of a lesion occurring at only one point in their course. I believe that acroparaesthesiae may occur as a symptom of either

(*i*) cervical spondylosis,
(*ii*) a costoclavicular syndrome involving particularly perhaps vasomotor elements,
(*iii*) compression of the median nerve in the carpal tunnel.

Acroparaesthesiae, however, are so common a symptom of cervical spondylosis that all patients who complain of them should have their necks *x*-rayed.

(2) *Pain referred to Myotome and Sclerotome.*—A dermatome is the area of skin supplied by a single spinal nerve. The importance of the dermatome in neurological diagnosis has perhaps tended to obscure the fact that a spinal nerve distributes sensory nerve fibres to muscles, bones, joints, and ligaments which have an anatomical distribution ranging widely beyond the cutaneous area innervated by the same segment. The muscles supplied by a single radicular nerve have been termed a myotome, and the bones and joints similarly supplied, a sclerotome. Pain due to irritation of a spinal posterior root or radicular nerve, therefore, may radiate widely, and this may sometimes give rise to difficulties in diagnosis. For example, both the 6th and 7th cervical radicular nerves supply sensory fibres to the posterior cervical muscles, pectoralis major, latissimus dorsi, and serratus magnus, as well as to other muscles of the trunk and upper limbs and the corresponding dermatomes. Irritation of either of these nerves may therefore cause pain referred to the neck, back, and front of the chest, as well as to the upper limb, and, it has been pointed out, may suggest pain of cardiac origin.

(3) *Muscular Wasting.*—This is not usually severe as a result of the radicular lesions of cervical spondylosis, but it may be a prominent symptom and may even occur in the absence of objective sensory abnormalities, when it may lead to an erroneous diagnosis of motor neurone disease. Frykholm points out that such muscular wasting is probably due to a selective damage to the anterior spinal roots by compression arising from the lower part of the foramina. It may affect the muscles supplied from several segments or from one only.

(4) "*The Frozen Shoulder.*"—Pain of radicular distribution due to cervical spondylosis and referred to the shoulder is not infrequently followed by the condition known as "frozen shoulder", in which gross limitation of active and passive movement of the shoulder occurs and any attempt to move the joint causes pain. The possibility that a "frozen shoulder" is a symptom of cervical spondylosis should always be borne in mind.

(5) *Acute or Subacute Multiradicular Symptoms.*—As a rule the radicular symptoms of cervical spondylosis are limited to one, or perhaps two, segments. The older clinical accounts of brachial neuritis, however, usually describe pain radiating down the whole length of the arm to all the digits and associated with some degree of generalized muscular wasting, weakness, diminution of

tendon reflexes, and perhaps very diffuse cutaneous sensory loss. This clinical picture may undoubtedly occur as the result of cervical spondylosis, even when the *x*-ray changes are limited to one or two intervertebral joints. As I have suggested above, the probable explanation is that in such cases root-sleeve fibrosis is much more widespread than the radiological changes would suggest, and that some change, perhaps a slight trauma or even possibly exposure to cold, has intensified the lesion in most of the roots from which the brachial plexus is derived. An alternative possibility is that an acute lesion of a single root may sometimes cause pain which, owing to the considerable overlap of dermatomes, radiates to a large area of the upper limb and at the same time reflexly interferes with muscular function.

Fig. 10.—Anterior aspect of spinal cord from same case as Fig. 5, showing indentation of cord and roots by osteophytes. (Kindly lent by Dr. M. I. P. Wilkinson.)

Pathogenesis of Myelopathy in Spondylosis

Cervical spondylosis damages the spinal cord less often than the nerve roots, but sufficiently often to make spondylotic myelopathy one of the commonest, if not the commonest, disease of the spinal cord during and after middle life. This is illustrated by the fact that 41 patients with cervical spondylosis have been admitted as in-patients to the neurological department of the London Hospital during the last 2 years, mostly on account of myelopathy. The pathogenesis of the myelopathy, like that of the root-sleeve fibrosis, is complex, and certainly a number of factors are concerned. The most obvious is direct compression of the cord by one or more protruding intervertebral disks (Fig. 10). When the disk protrusion is large, the cord may be compressed between it and the laminae posteriorly, the pressure being sufficient even to cause thinning of the laminae. Greenfield (1953), however, believes that in the majority of cases the areas of demyelination are too limited to be explained as the result of simple compression. He thinks that compression may operate indirectly by interfering with the blood flow through the anterior spinal artery. The blood supply to the spinal cord may be further impaired by narrowing of the intervertebral foramina through which the radicular arteries penetrate. Compression of the anterior spinal veins has also been regarded as a contributory factor. Stretching of the ligamenta denticulata also, in Greenfield's opinion, plays an important part, since these ligaments tend to increase the affects of compression on the anterior spinal vessels by anchoring the spinal cord. Moreover, they exert tension on the lateral aspects of the spinal cord. The neck, however, is not static, but in constant movement throughout waking life, and a considerable amount of movement still occurs in a spine which is the site of severe spondylosis. As already mentioned, movement may be pathological when one body slips forward upon the one immediately below it on flexion of the neck. Root-sleeve fibrosis which is invariably present to a greater or less extent in these cases, tends to anchor the roots in the foramina and, by thus limiting the mobility of the cervical cord, must add to the traumatic effect of repeated movement of the neck when the cord is already compressed by a disk protrusion. All these factors combine to produce a condition which is best described as cervical myelopathy. Moreover, in the presence of cervical spondylosis, even though the spinal cord has so far apparently escaped injury, severe damage may be produced by forcible extension of the neck; such extension may result from a blow upon the front part of the head, or may even occur, as Symonds has recently shown, during the administration of anaesthetic or an operation upon the tonsils.

Symptomatology of Cervical Myelopathy due to Spondylosis

I do not propose to discuss in detail the symptomatology of cervical myelopathy resulting from spondylosis (Brain, 1948; Brain and others, 1952),

but only to draw attention to the relationship between the pathology described above and the symptomatology, and, in particular, to try to show how the pathology explains the extremely varied clinical picture. To simplify matters, let us consider only the factor of disk protrusion. Since these protrusions may be single or multiple, and may occur at any, or every, level of the intervertebral disks, it is clear that any segment of the cervical cord may be compressed from the 3rd to the 8th, that is, either above or in the course of the cervical enlargement. Furthermore, a disk protrusion into the vertebral canal may be situated either in the mid-line or to one or other side, or may be more or less continuous, and, except in extreme cases, the resulting demyelination does not involve the whole transverse extent of the cord. It is therefore easy to understand how varied is the resulting clinical picture and how many other disorders it may simulate. Since the onset of symptoms is usually insidious, and may be either intermittent or steadily progressive, the disorder will tend to resemble other lesions of the spinal cord which occur in middle life and have these general characteristics. Muscular wasting, fasciculation and weakness in the upper limbs, and spastic weakness of the lower limbs in the absence of sensory loss, may closely simulate motor neurone disease. Weakness, numbness, and clumsiness of the upper limbs, associated with ataxic paraplegia, and perhaps some sensory loss in the lower limbs, present a clinical picture resembling that of disseminated sclerosis. When the damage falls chiefly upon the pyramidal tracts and the posterior columns, with which may be associated some wasting of the hands and sensory loss of glove distribution in the upper limbs, there is a considerable resemblance to sub-acute combined degeneration. Extramedullary tumour, intramedullary tumour, and syringomyelia may all easily be simulated. When the symptoms are those of pure bilateral pyramidal degeneration, a diagnosis of primary lateral sclerosis may be made. In some cases cervical myelopathy may for a long time cause only paraplegia without detectable abnormalities in the upper limbs, and then the cause may be thought to originate in the dorsal region of the spinal cord. Occasionally, as Symonds (1953) has recently pointed out, cervical spondylosis may be the cause of quadriplegia of sudden onset, which may be permanent or, as in one recent patient of my own, brief and intermittent. Finally, to add to the hazards of diagnosis, not only may cervical spondylosis co-exist with a quite independent lesion of the nervous system which is itself responsible for the symptoms, but it may sometimes be associated with other abnormalities of the spine or spinal cord, particularly of congenital origin, such as congenital fusion of vertebrae, cervical spina bifida, and the Arnold-Chiari malformation, while syringomyelia and tabes may cause a cervical anthropathy which is not only difficult to distinguish from spondylosis, but may actually be complicated by it.

Thoracic Intervertebral Disk Protrusion

I am inclined to include thoracic intervertebral disk protrusions rather among the unknown than among the known facts of spondylosis. They are certainly far less common than disk protrusions at the cervical and lumbar regions, presumably for mechanical reasons. The neurologist and neurosurgeon are familiar with them as rather uncommon causes of extramedullary compression of the spinal cord. I have sometimes suspected one as the cause of an otherwise unexplained root pain, but, apart from those causing compression of the spinal cord, I have never been able to demonstrate one by myelography. This is a field which I am sure would repay research. Apart from the presence of thoracic disk protrusions sufficient to cause symptoms, I have also encountered a good many patients suffering from progressive paraplegia in association with severe thoracic spondylosis. The opportunity for the pathological investigation of such cases rarely occurs. I have suspected that the narrowing of the intervertebral foramina by interfering with the vascular contribution which the radicular arteries make to the vasocorona of the spinal cord may contribute to an ischaemic myelopathy. Here, also, pathological research might prove rewarding.

Lumbar Disk Protrusion and Foraminal Pressure Neuritis

I have left lumbar spondylosis until the last because it has been the subject of research for a much longer period than cervical spondylosis, and because, until recently at least, much more has been known about it. This, however, does not mean that there are not still many important unknown factors. It is desirable to bear in mind that the distinction between nuclear and annular protrusions, which I discussed in connexion with cervical disks, applies equally to those in the lumbar region. There are, however, certain points of difference between the two. In the lumbar region acute nuclear protrusions are a much commoner cause of symptoms than at the cervical level, but it is probable that in the lumbar region pre-existing disk degeneration is a more important predisposing cause of such nuclear protrusion than it is in the neck. At the lumbar level, as at the cervical

a nuclear protrusion, if undisturbed, may provoke an osteophytic reaction from the vertebral bodies, which may in the end be difficult to distinguish from an annular protrusion. In particular, plain *x* rays may provide no clue whether a narrowed lumbar intervertebral disk space results from simple disk degeneration, annular protrusion, or nuclear protrusion.

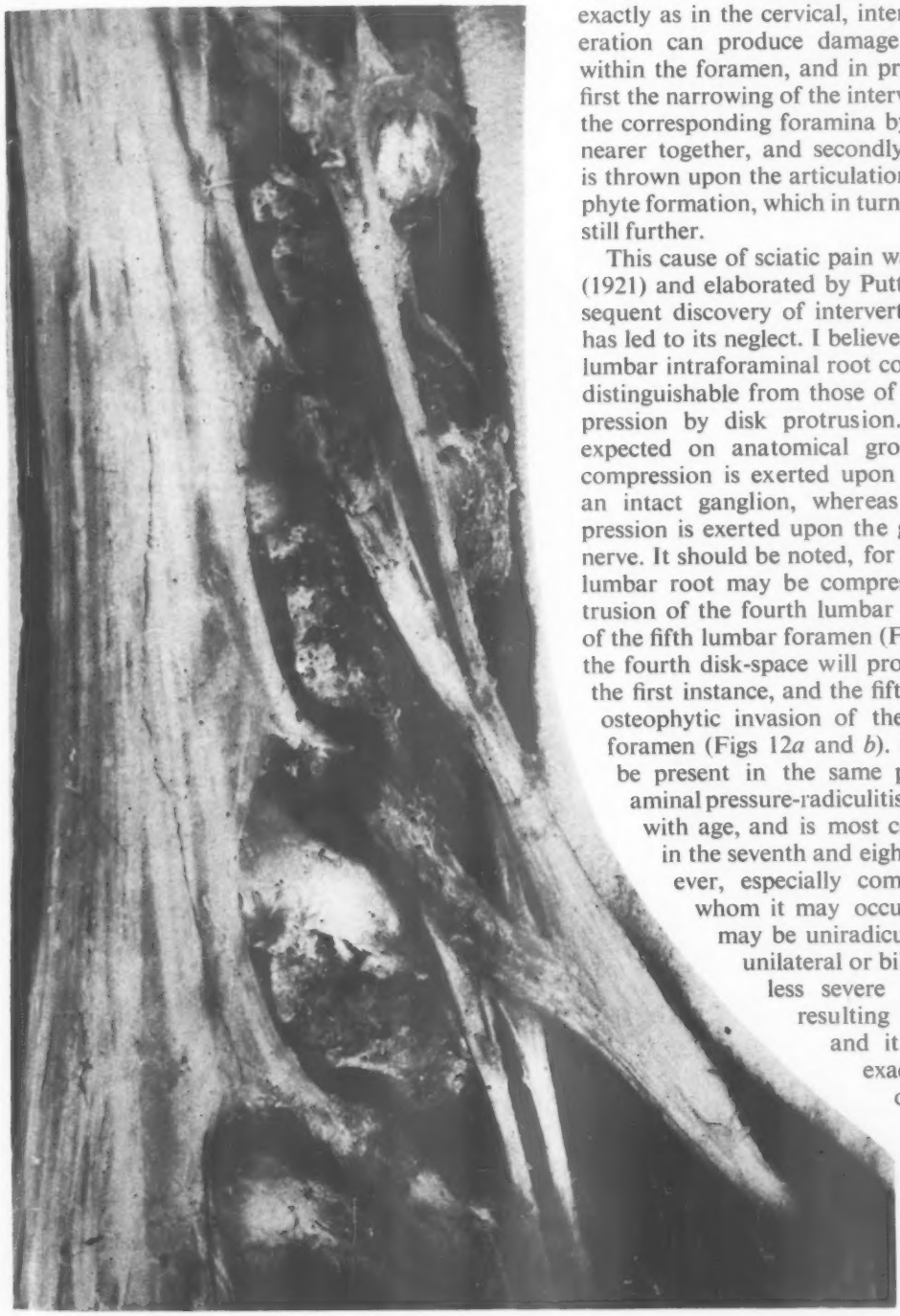
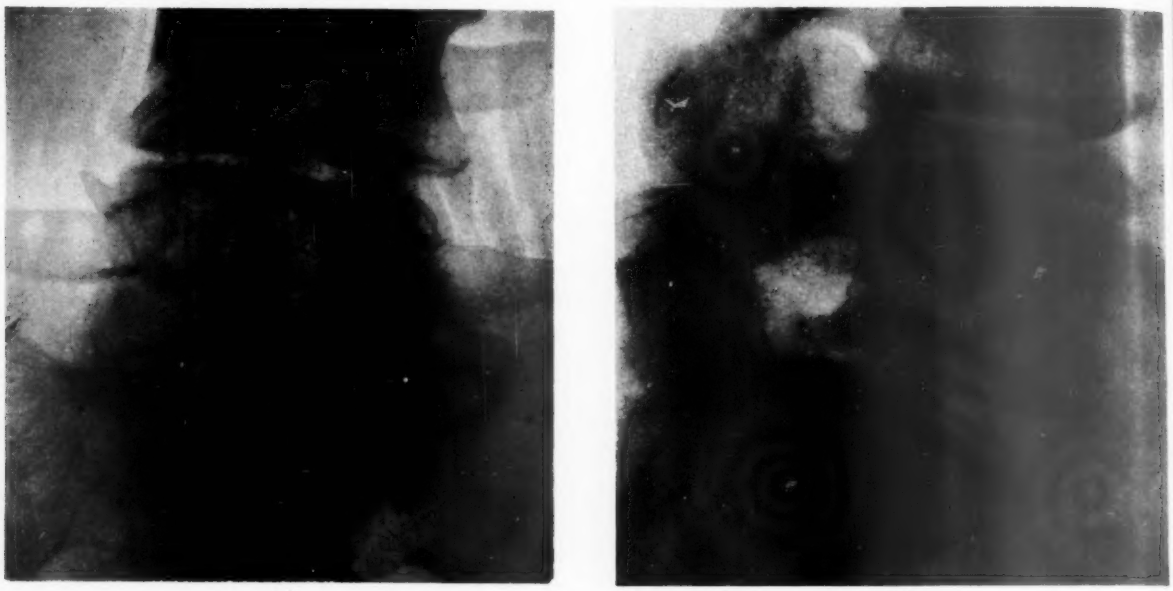


Fig. 11.—Dissection of lumbar nerve-roots (L2-L5). The lowest (5th) can be traced up from the lumbo-sacral disk, to where, intradurally, it passes behind the 4th lumbar disk (Dr. R. J. Harrison).

Whereas in the neck, compression of spinal nerve roots by disk protrusion in the vertebral canal is rare compared with compression in the foramina, the reverse is generally thought to be the case at the lumbar level. Nevertheless, in the lumbar spine, exactly as in the cervical, intervertebral disk degeneration can produce damage to the spinal nerve within the foramen, and in precisely the same way, first the narrowing of the intervertebral disk narrows the corresponding foramina by bringing their edges nearer together, and secondly an additional strain is thrown upon the articulation, so leading to osteophyte formation, which in turn narrows the foramina still further.

This cause of sciatic pain was hinted at by Sicard (1921) and elaborated by Putti (1927), but the subsequent discovery of intervertebral disk protrusion has led to its neglect. I believe that the symptoms of lumbar intraforaminal root compression are usually distinguishable from those of intrathecal root compression by disk protrusion. This is only to be expected on anatomical grounds, for intrathecal compression is exerted upon the posterior root of an intact ganglion, whereas intraforaminal compression is exerted upon the ganglion or the spinal nerve. It should be noted, for example, that the fifth lumbar root may be compressed either by a protrusion of the fourth lumbar disk or by narrowing of the fifth lumbar foramen (Fig. 11). Radiologically the fourth disk-space will probably be narrowed in the first instance, and the fifth in the second, with osteophytic invasion of the L5-S1 intervertebral foramen (Figs 12*a* and *b*). Of course, both may be present in the same patient. Lumbar foraminal pressure-radiculitis increases in frequency with age, and is most commonly encountered in the seventh and eighth decades. It is, however, especially common in diabetics, in whom it may occur at an earlier age. It may be uniradicular or multiradicular, unilateral or bilateral. Pain is usually less severe than in the sciatica resulting from disk protrusion, and it is less likely to be exacerbated by coughing or sneezing; it is often, however, influenced



(*a*) (*b*)

Fig. 12 (*a* and *b*).—Lumbar spondylosis causing narrowing of 5th lumbar disk-space and foramen. Antero-posterior and lateral views. (Kindly lent by Dr. M. Jupe.)

by posture and may be worse when the patient is sitting. On the other hand, there may be no pain, but only dyaesthesiae in the distribution of the dermatomes supplied by the affected root or roots. Cutaneous sensibility is often blunted over these areas. When several roots are involved there may be conspicuous muscular weakness, wasting associated with fasciculation, and diminution or loss of the knee jerks.

Look back for a moment and recall that it is just 20 years since sciatica was first attributed to an intervertebral disk protrusion. Before that it was called sciatic neuritis and put down to various hypothetical toxins. Even then the same view was taken of brachial neuritis, and nothing at all was known of the protean clinical picture of spinal cord compression by disk protrusion, except for a small number of cases gathered by neuro-surgeons in which the lesion was called a chondroma. How much we have learned since then! But how much still remains to be discovered!

I am grateful to Dr. R. J. Harrison for the dissections illustrated in Figs 3 and 11.

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HEREDO-FAMILIAL VASCULAR AND ARTICULAR CALCIFICATION

BY

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(RECEIVED FOR PUBLICATION JANUARY 4, 1954)

This report concerns a family, several members of which display an unusual type of calcification of joint structures and arteries, calcification and ossification of ligaments, and juxta-articular and periosteal new bone formation.

The full syndrome is a readily recognizable clinical entity and appears to be rare, since only two previous reports of similar cases have been traced in the literature. Magnus-Levy (1914) described a patient, a 47-year-old German female, who gave a history of recurrent attacks of painful joint swellings, starting in her teens in isolated fingers and later involving the hands and elbows. Each attack was followed by firm enlargement of the affected joints. She later developed intermittent claudication in the legs and evidence of heart failure. The joints of the fingers were enlarged, there was extensive thickening and tortuosity of the larger limb vessels, and radiologically there were calcifications in relation to the olecranon, patella, and finger joints, and the thickened vessels showed heavy calcification of an unusual pattern.

Levitin (1945) reported the case of a 24-year-old American serviceman who complained of painful swelling of the joints of the hands and pain in one knee of 2 weeks' duration. He also had painless swelling of the finger joints and nodular thickening of the arteries of the limbs and the tongue, but there was no obvious abnormality of the peripheral circulation. The radiological changes closely resembled those in Magnus-Levy's patient.

Case Reports

Case 1. A 47-year-old taxi-driver complained of attacks of painful swelling in the hands and feet, stiffness of the back, and pain in the calves on walking.

He gave a history that about 20 years ago he suddenly developed pain and swelling of the dorsum of the right hand with heat and redness of the overlying skin. Over the next few days the wrist and fingers became affected, the whole region being uniformly swollen. Moderate spontaneous pain was present, and movement of the wrist and fingers was excruciatingly painful. The attack gradually subsided in about 4 weeks, leaving slight residual enlargement of the wrist and finger joints. Some months later, an identical attack occurred in the left hand and similar milder attacks were noted subsequently in the feet and on one occasion in the right elbow. He had not felt ill, and did not think that he had been febrile during these episodes. The attacks, always confined to one site, occurred at irregular intervals of about 2 to 6 months, and each attack left further joint enlargement in the affected region with some limitation of movement. During the past 10 years or so, the attacks had been much milder, involving one or sometimes two or three adjacent fingers, and small transitory painful lesions had developed at new sites, particularly over such bony prominences as the ischial tuberosities and heels, and once over the manubriosternal region. In addition, he had noted occasional aching in the larger joints, particularly the knees and shoulders.

About 10 years ago, following forcible extension of the spine in a road accident, he was troubled for a few weeks by aching in the thoracic region of the back, and since then had noted progressive stiffening of the back and neck and had developed a slight stoop. Only in the past few months had he had any further back pain, this time at the base of the neck. Some 2 years ago, pain typical of intermittent claudication developed in the calves, both being affected at the same time. The pain was initially brought on by walking about half a mile, but the pain-free distance has gradually decreased to about 100 yards, the progression of symptoms on the two sides being exactly parallel.

Although he had gradually lost about 2 stones (12·7 kg.) in weight since the first symptoms, his general health had remained good and he had no other symptoms. His only past medical history was of an attack of left-sided ophthalmic herpes zoster 11 years previously.

His sister, he said, had suffered similar attacks of painful swelling in the hands with residual enlargement of the finger joints. He knew of no other family history of similar disease.

Examination.—He was a healthy-looking, sparely-built man, who stood with about 30° total flexion deformity, due to a smooth, fixed lumbo-thoracic kyphos;

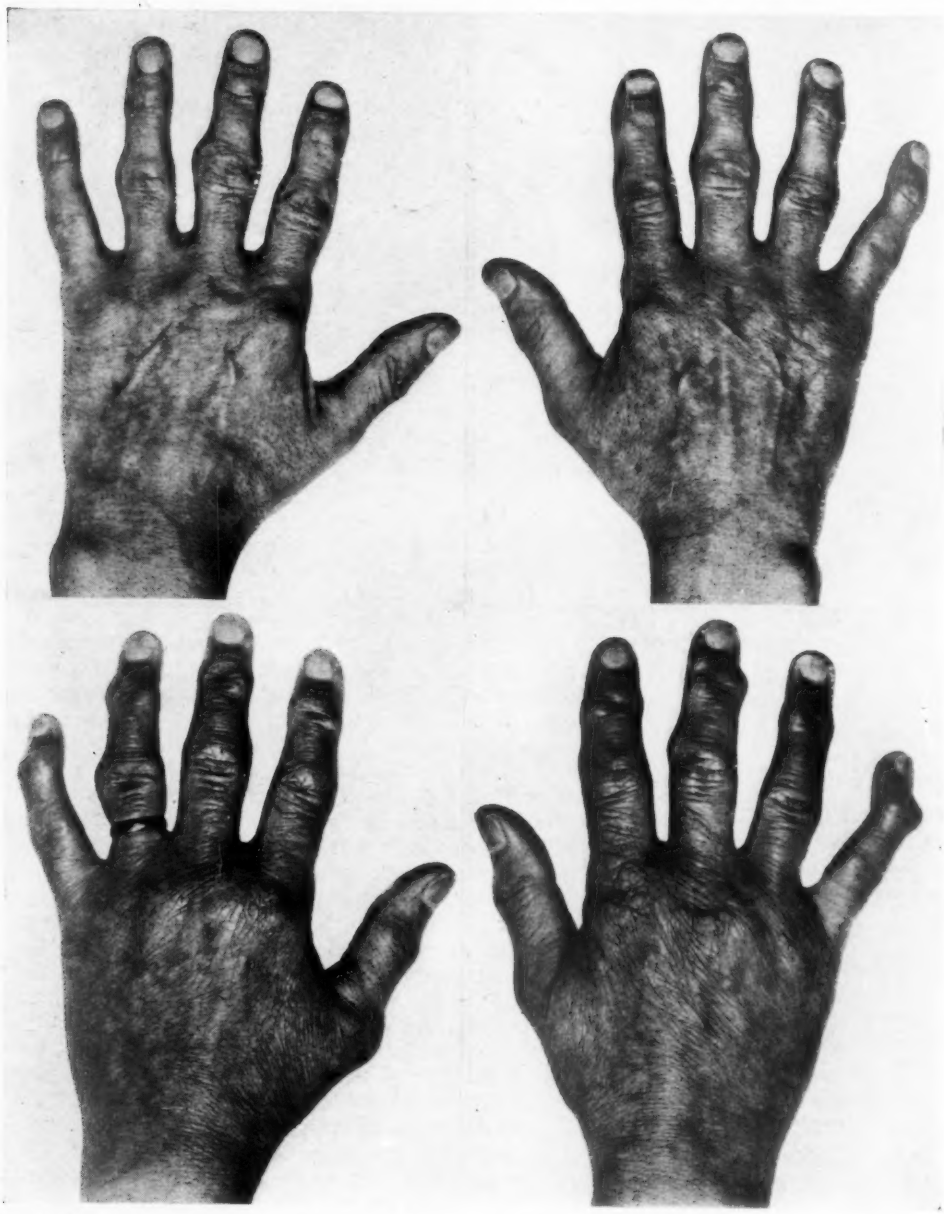

Fig. 1(*a*).—Case 1, showing asymmetrical, largely bony enlargement of finger joints.

Fig. 1(*b*).—Case 2, showing more marked similar changes.

he had between a quarter and a half of the normal range of neck movement. Chest expansion was 3·5 cm.

The texture, temperature, and sweating of the skin of the extremities was normal. The joints of the fingers (Fig. 1*a*) showed striking bony enlargement, and around the fifth metacarpo-phalangeal and fourth and fifth proximal interphalangeal joints of the right hand, which had been the site of a mild flare-up some weeks previously, there was also slightly tender soft tissue thickening; the remaining hand joints were not tender. There was moderate mechanical limitation of finger movement but hand function was good. The first carpo-metacarpal joints were not enlarged, but their motion was slightly limited and accompanied by crepitus. The wrists showed moderate restriction of movement and there was a slight flexion deformity of the elbows. The sternoclavicular and manubriosternal joints were slightly enlarged and tender, and the movement of both shoulder girdles was slightly restricted. The toes were normal apart from dorsal subluxation of the outer metatarso-phalangeal joints on the left. The tarsi showed a valgus deformity and slight limitation of movement. There was slight bony enlargement of ankles and knees with crepitus on motion of the latter. Hip movement was full and painless, and straight-leg raising was to 90° on each side. Both ischial tuberosities were slightly tender.

Palpable nodular thickening of the radial, brachial, femoral, and left superficial temporal arteries was present; dorsalis pedis and posterior tibial pulses were absent on both sides, these vessels being impalpable. The retinal vessels appeared normal. Oscillometry showed greatly diminished pulsations in both calves and in the upper limbs the flush of reactive hyperaemia (Pickering, 1933) appeared at the tips of the digits of the left hand in 4 seconds, and at the tip of the right thumb in 5 seconds and of the right fingers in 7 seconds.

There was some pallor of the conjunctivae; no abnormality was noted in the viscera or lymph glands. Apart from anaesthesiae over herpes scars, in the left frontal region, no abnormality was detected in the nervous system.

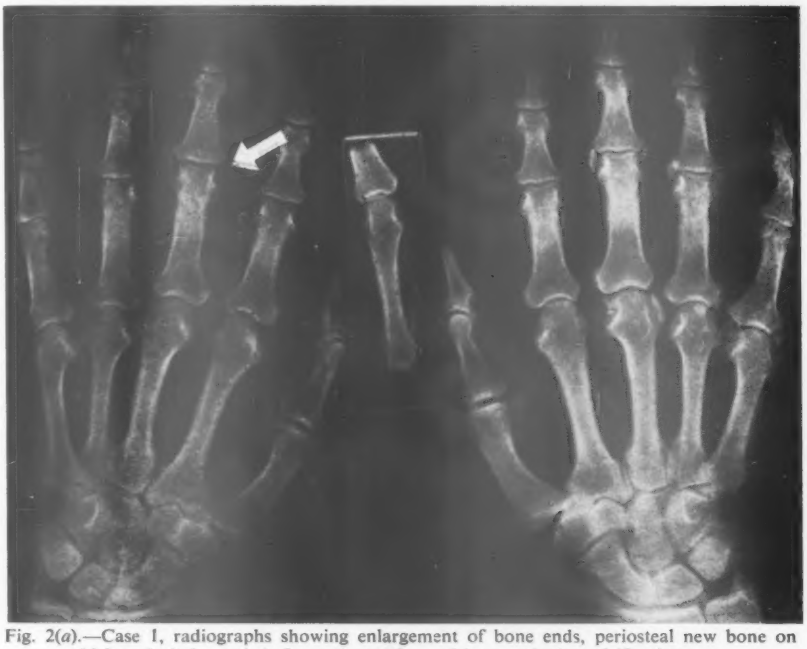

Fig. 2(*a*).—Case 1, radiographs showing enlargement of bone ends, periosteal new bone on thickened phalangeal shafts, and capsular and intra-articular calcification.

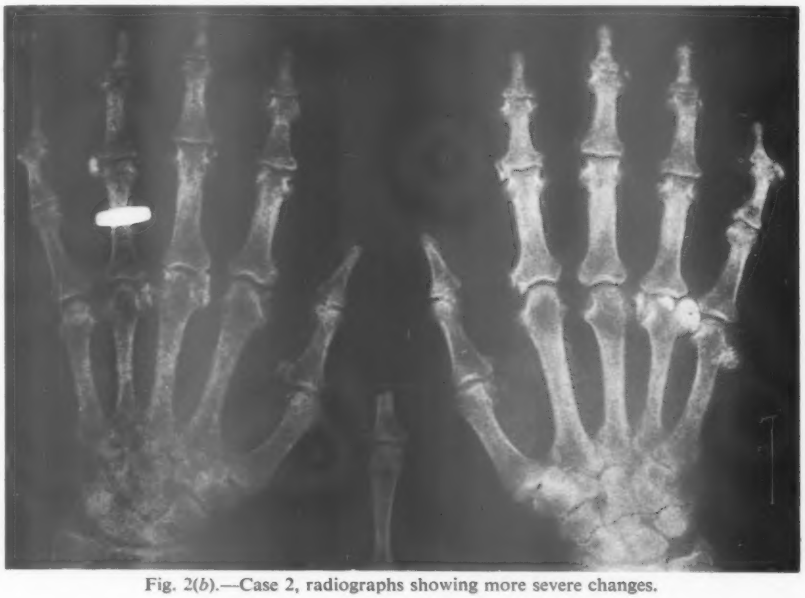

Fig. 2(*b*).—Case 2, radiographs showing more severe changes.

Radiological Investigations.—The appearances were most unusual. The hands (Fig. 2*a*) showed enlargement and rather widely-spaced trabeculation of the ends of the metacarpals and phalanges with asymmetrical deposition of new bone, mainly at a short distance from the articular surface; the shafts of the phalanges appeared thickened probably because of the incorporation of periosteal new bone which was evident on several (particularly on both the fifth proximal) phalanges. This irregular new bone formation resulted in the false appearance of "erosions" of several metacarpal heads (notably the right fifth), and of the bases of both fifth proximal phalanges. The joint spaces proper were normal throughout, but in some of the terminal interphalangeal joints the growths of new bone had approximated at the joint margins, giving a spurious appearance of narrowing. Amorphous depositions of calcium were present in close relation to almost all the finger joints. The appearance suggested that the calcification was in some cases intra-articular and in others in joint capsules (Fig. 3*a*, overleaf). Calcium deposits were present in relation to both first carpo-metacarpal joints, and there was deposition of irregular new bone on the lower ends of both ulnae. Radiographs (Fig. 5*a*, overleaf) confirmed the subluxation of the outer metatarso-phalangeal joints on the left, and suggested enlargement of the metatarsal heads and bases of the proximal phalanges. There was definite erosion of the heads of the left third, fourth, and fifth metatarsals, with probable narrowing of the fifth metatarso-phalangeal joint space. Calcification, of lesser degree but of the same type as the fingers, was visible in relation to several metatarso-phalangeal and interphalangeal joints, and faintly calcified vessels were visible in both first interosseous spaces. Irregular new bone was present on both medial cuneiform bones, and, in the lateral view, bony spurs were present on the plantar surface of each os calcis. Anterior and posterior tibial arteries on both sides

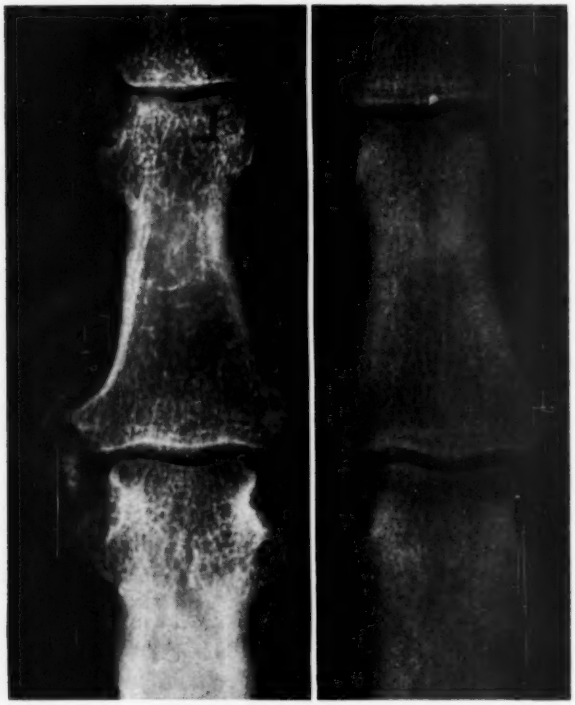

Fig. 3(*a*).—Case 1, enlargement of area indicated by arrow in Fig. 2(*a*), showing bony enlargement and articular calcification.

Fig. 3(*b*).—Normal control.

showed heavy clumpy calcification. New bone was present on both femoral condyles (Fig. 4*a*), and faint spotty calcification in relation to the lateral compartment of the right knee. The striking feature of the films depicting the knee joints was, however, the gross clumpy calcification of both popliteal arteries, and the fainter calcification of an unusually tortuous long saphenous vein on the left side. Radiographs of the calves showed that the calcification continued in the anterior and posterior tibial and peroneal arteries.

New bone formation was evident on the epicondyles of the left humerus, there were small soft tissue calcifications in relation to both elbow joints, and on each side the proximal portion of an interosseous artery was faintly calcified.

New bone was also present on the upper aspect of the right greater trochanter (Fig. 6*a*); the hip joints appeared normal. The pelvis was asymmetrical and was tilted backwards because of the kyphos, and both ilia appeared to be more vertical than normal, and to be thickened above the acetabulum. There appeared to be new bone formation over both ischial tuberosities, and, on the left, this partly surrounded a translucent area which may in part have resulted from bone erosion. The left sacro-iliac joint appeared fused, whereas on the right some joint space was retained, though the margins were sclerosed and irregular. A good joint space was visible at the symphysis pubis, where the appearances otherwise resembled those of the right sacro-iliac joint. Clumpy

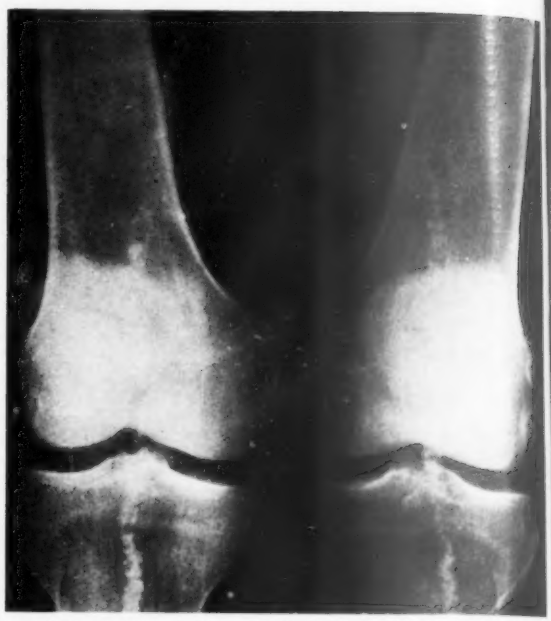

Fig. 4(*a*).—Case 1, radiograph illustrating new bone on femoral condyles, faint calcification in relation to lateral compartment of right knee, heavy calcification of popliteal arteries, and faint calcification of left long saphenous vein. (Two lead pellets also present near right knee.)

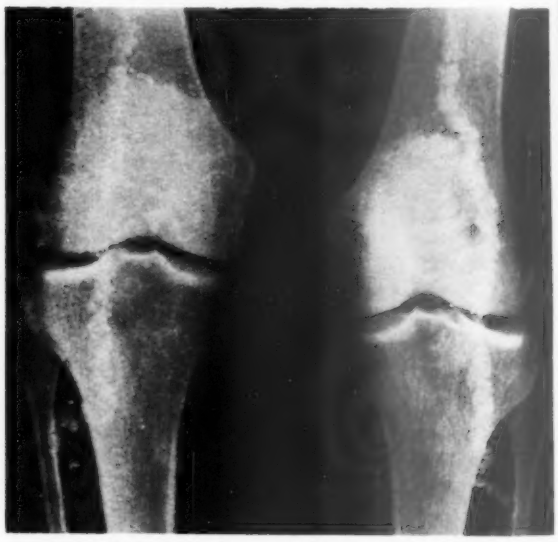

Fig. 4(*b*).—Case 2, radiographs showing similar changes.

calcification was visible in vessels in the pelvis and upper thighs, probably the gluteal, femoral, and profunda femoris arteries and some of their branches; these vessels appeared rather wider than normal.

The appearance of the lumbar spine on antero-posterior projection (Fig. 7) resembled the "bamboo spine" of advanced ankylosing spondylitis, but, in the lateral view (Fig. 8*a*), in spite of extensive ligamentous ossification, there was none of the characteristic squaring of the vertebral bodies, and the vertebral plates appeared

to be duplicated. The anterior aspect of the lower abdominal aorta was faintly outlined by a fine streak of calcification. Multiple small calcifications were visible in the upper abdomen, probably in visceral vessels. There was wedging of the eighth thoracic body (Fig. 9*a*) and anterior osteophytosis of the adjacent bodies at the T8/9 space. The T9/10 space was fused anteriorly at, or just anterior to the disk margin. At the posterior ends of the disk spaces, there appeared to be bony continuity between most of the vertebral bodies. Calcification was visible in the disk substance of the T6/7 space and, in lesser degree, in the T9/10 and T10/11 disks.

In the cervical spine the upper disk spaces were normal, but the C2/3 space was almost sealed anteriorly by beak-shaped overgrowths of the corresponding bodies, resembling osteophytes. At the site corresponding to these growths on the anteroinferior margin of the fourth cervical body, a small, oval amorphous calcification was lying in contact with the vertebra. Apart from slight spondylosis at the C7/T1 level, the cervical spine appeared otherwise normal. Extensive clumpy calcification was visible in vessels, probably medium-sized arteries, in the front of the lower neck.

The skull was normal. The pineal body was calcified. Multiple calcifications, probably within costal cartilages were seen on the radiograph of the chest but there was no definite calcification of the pulmonary vessels. There was erosion of several ribs, of the type seen in coarctation of the aorta.

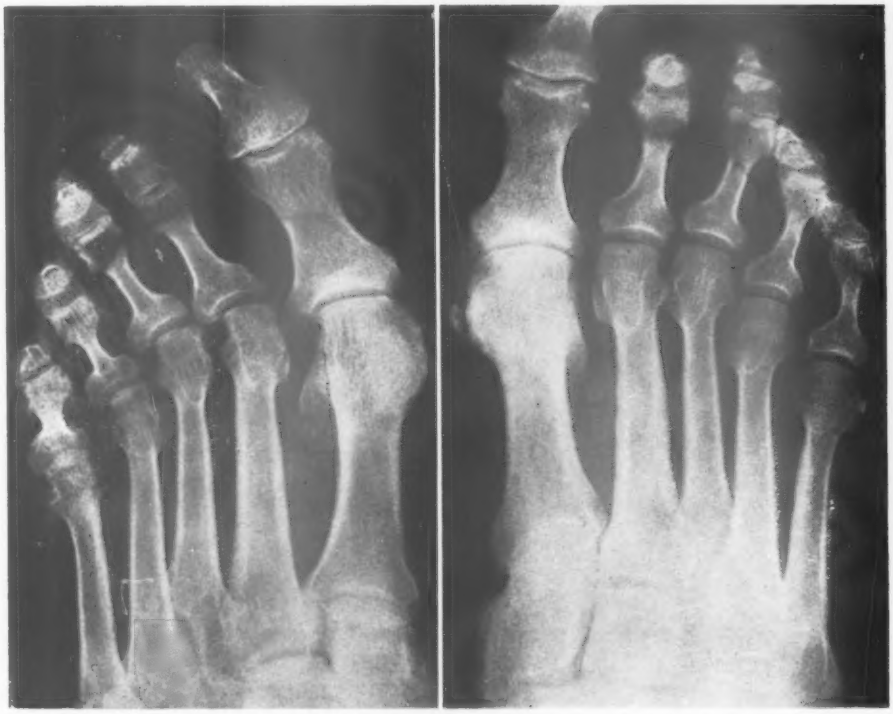

Fig. 5(*a*).—Case 1, radiograph showing subluxation of outer metatarso-phalangeal joints and erosion of outer metatarsal heads of left foot, small calcifications in relation to metatarso-phalangeal and interphalangeal joints, and faintly calcified first metatarsal arteries.

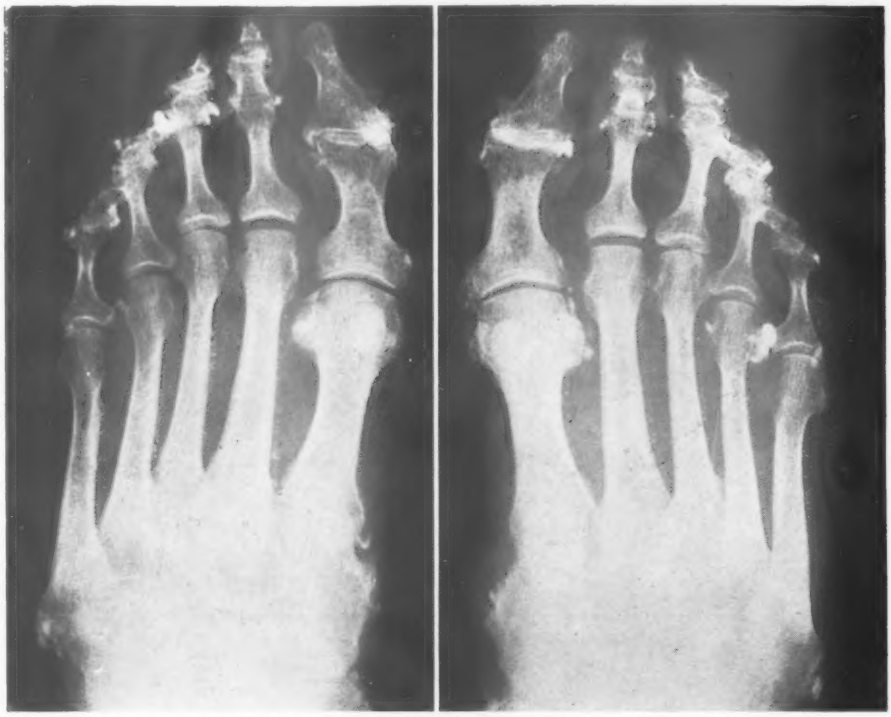

Fig. 5(*b*).—Case 2, showing slight porosis of outer metatarsal heads and extensive articular calcifications.

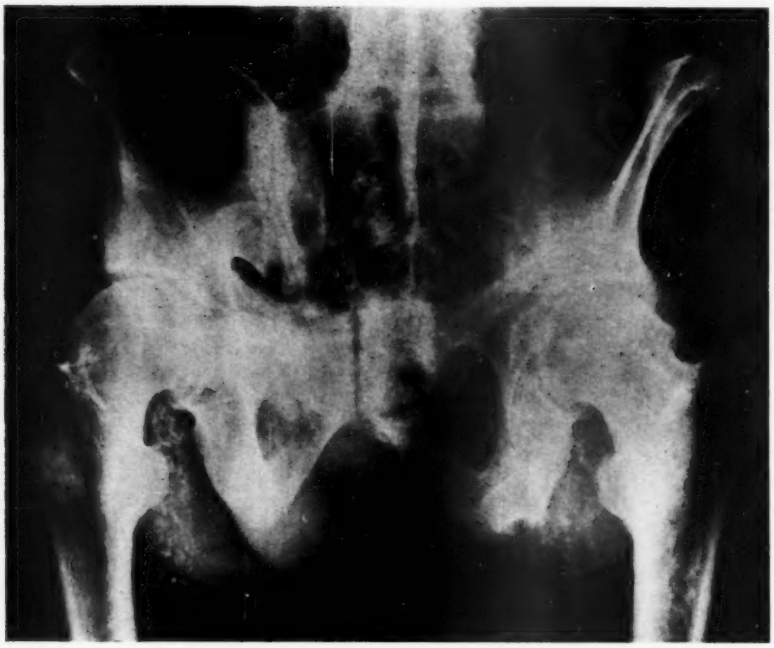

Fig. 6(*a*).—Case 1, radiograph showing asymmetry of pelvis, new bone formation on right greater trochanter and ischial tuberosities, fusion of left and narrowing of right sacro-iliac joint with sclerosis and irregularity of the margins of the latter and of the symphysis pubis. Heavy calcification is visible in gluteal, femoral, and profunda femoris arteries and some of their branches.

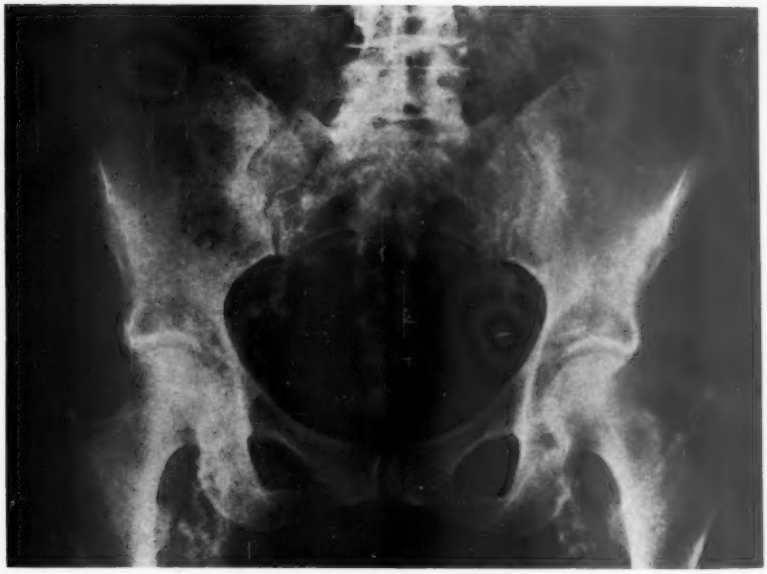

Fig. 6(*b*).—Case 2, radiograph of pelvis, showing similar but less marked asymmetry, periosteal new bone on greater trochanters and anterior superior iliac spines, and heavy calcification of iliac, femoral, and profunda femoris arteries.

Laboratory Investigations.

Haemoglobin 70 per cent. (10·4 g./100 ml.).

Haematocrit 35 vols./100 ml.

Mean corpuscular haemoglobin concentration 30 per cent.

White blood cells 8,600/c.mm.

Differential count normal.

Serum calcium 9·6 mg./100 ml.; Serum phosphorus 3·1 mg./100 ml.; Serum alkaline phosphatase 17 units/100 ml. (on two occasions); Serum uric acid 3·1 mg./100 ml.; Serum cholesterol 110 mg./100 ml.; Serum bilirubin 0·5 mg./100 ml.; Serum thymol turbidity 2·4 units.

Plasma cholesterol 597 mg./100 ml.; Plasma alkali reserve 71 vols. CO_2/100 ml.; Serum albumin 3·8 g./100 ml.; Serum globulin 2·5 g./100 ml.

Serum protein electrophoresis: albumin normal, $\alpha_1$globulin normal, $\alpha_2$globulin moderately increased, β globulin moderately increased, γ globulin normal.

Urine: albumin free, neutral or acid, specific gravity 1,020, centrifuged deposit normal, culture sterile; Urea clearance 97 per cent. average normal; Plasma urea 30 mg./100 ml.; Urine amino-acid nitrogen 382 mg./24 hrs; Urine amino-acid paper chromatography, normal pattern; Urinary calcium excretion 191 mg./24 hrs (on ward diet giving an approximate daily intake of 1,200 mg. calcium).

Blood Wassermann reaction negative.

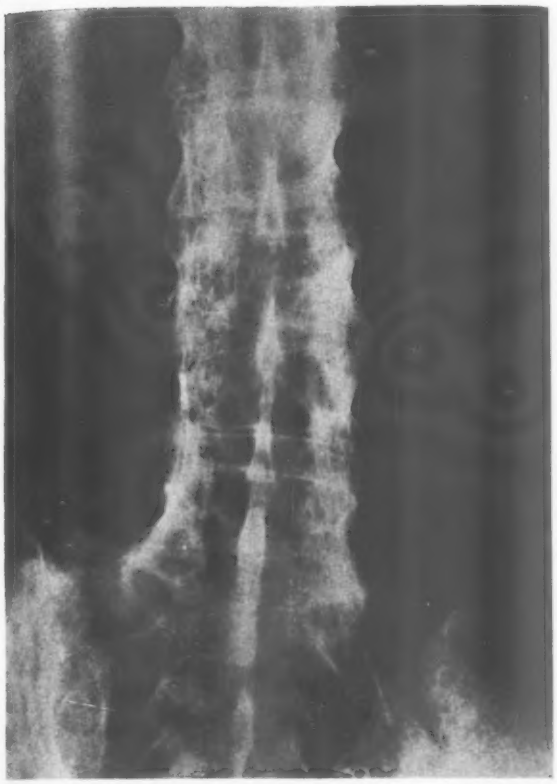

Fig. 7.—Case 1, radiograph of ankylosed lumbar spine with extensive ligamentous ossification.

Electrocardiogram normal.

Blood sedimentation rate varied between 30/200 mm. and 16/200 mm. (Westergren) during 6 weeks' observation.

Rose's serum differential agglutination test (modified Ball, 1950) at weekly intervals, gave negative results on the first two occasions and positive results on four occasions thereafter.

Arteriography *via* right brachial artery showed all digital arteries patent.

Case 2. Sister of Case 1, a housewife, aged 50 years, stated that at the age of 19 she had pain in the manubriosternal region for about one month, particularly on coughing or sneezing. Her next symptom occurred 20 years ago, when she developed a painful swelling involving the whole right upper limb, and the swelling subsided in about 3 weeks. During this attack she was not ill, and she was disturbed only by the pain. An identical attack occurred in the left hand 2 weeks later, and subsequently she had similar attacks in the hands at intervals of one to two years, both hands being sometimes affected simultaneously. These attacks sometimes involved the fingers, and after each attack she noted some enlargement of the affected finger joints with a little limitation of movement. She thought that a course of gold injections given about 13 years ago was of benefit, and during the past 10 years or so the attacks had been much milder and confined to isolated finger joints.

Some 10 years ago she also developed typical intermittent claudication simultaneously in both calves on brisk walking. Shortly after this, she began to lose weight, became pale and breathless, and noted an increase of a chronic, slightly productive cough to which she had been subject for a number of years. Eventually, 7 years ago, pernicious anaemia was diagnosed, liver injections were given with apparent benefit, and she regained her normal weight. In spite of the improvement in the anaemia, the claudication persisted, and the distance she could walk briskly without pain had gradually decreased to about 200 yards.

Her first symptoms in the feet were noted 2 years ago; these consisted of aching across the dorsum of the forefoot on walking and attacks of burning discomfort in the soles in bed. The latter attacks were particularly severe in winter; they were eased by movement of the feet and relieved by walking about.

She had never had any trouble with the back, and had noted no other symptoms other than occasional hot flushes since the menopause 3 years ago. In her past history she recalled "growing pains" in the lower limbs, which ceased at about 10 years of age, but no serious illnesses.

Fig. 8(*a*).—Case 1, lateral radiograph of lumbar spine, illustrating duplicated vertebral plates and lack of squaring of vertebral bodies.

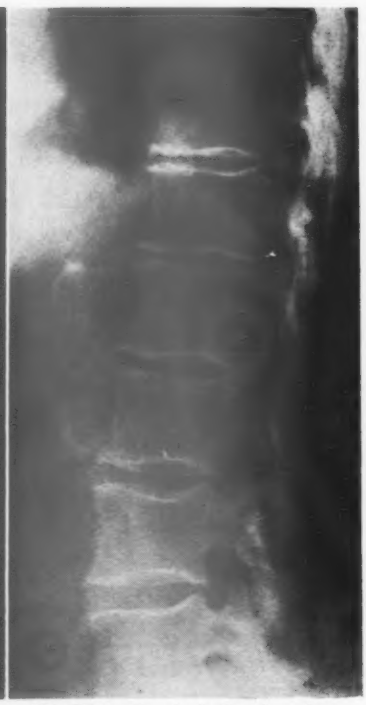

Fig. 8(*b*).—Case 2, similar view, showing only slight porosis and minor osteophytosis of vertebral bodies.

Fig. 9(*a*).—Case 1, lateral radiograph of thoracic spine, showing wedging of 8th thoracic body, bony continuity between several vertebral bodies posteriorly, anterior osteophytosis at T8/9 and fusion at T9/10 spaces, and calcification in substance of disks T6/7, 9/10 and 10/11.

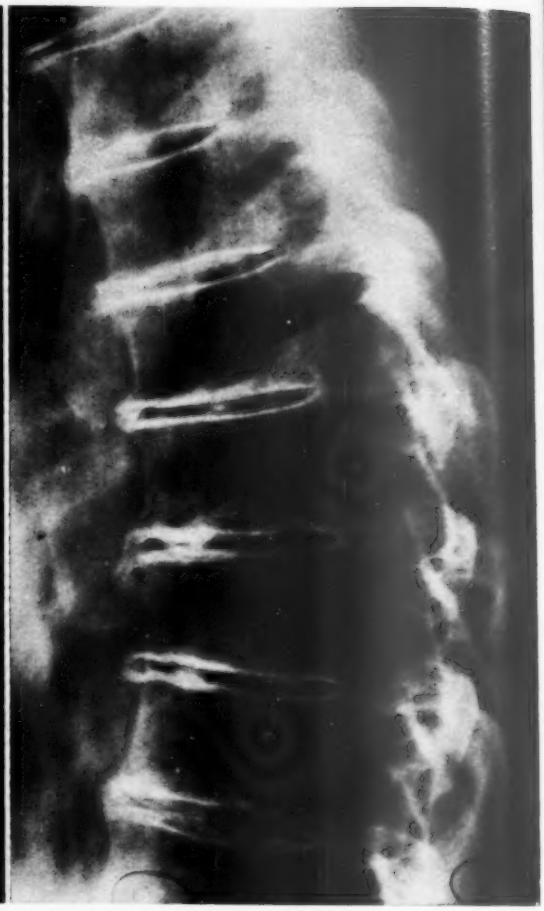

Fig. 9(*b*).—Case 2, radiograph of thoracic spine, showing calcification at disk margins and a small deposit in the substance of disk T8/9.

Examination.—She was a pale, well-nourished woman, bearing some facial resemblance to her brother, Case 1. Her hands (Fig. 1*b*), which were of normal temperature, colour, and moisture, were strikingly similar to his, with even more marked non-tender enlargement of the finger joints, the asymmetrical bony excrescences in some cases extending beyond the joint limits; there was flexion deformity of the terminal interphalangeal joints of both fifth fingers, and moderate limitation, apparently mechanical, of the others. The metacarpo-phalangeal joints showed rather less bony enlargement than the interphalangeal joints, and there was slight rubbery soft tissue thickening of both. Slight bony enlargement of both first carpo-metacarpal joints was present, with some crepitus on movement. The lower ends of the right radius and ulna and of the left ulna to a lesser extent were enlarged, and there was slight limitation of wrist movement. The external condyle of the right humerus felt slightly enlarged; both elbows lacked 5-10° extension. Both shoulder girdles were considerably limited in movement, scapulo-humeral movement being full. In the feet there was a little slightly tender soft tissue thickening of the outer metatarso-phalangeal joints and additional slight bony enlargement of both first metatarso-phalangeal joints. The bases of the first and fifth metatarsals on each side were enlarged. The tarsi were normal, but there was slight limitation of movement at the right ankle. The right Achilles tendon was a little thickened and tender, and there were palpable bony spurs on each os calcis lateral to the insertions of the Achilles tendons. The bones around both knee joints felt rather prominent and were generally tender, and there was palpable irregularity of the upper outer aspects of both patellae. Terminal knee flexion was slightly painful on both sides. Hip movement was full and painless.

The lumbar spine was somewhat straightened and there was a slight thoracic kyphos. In the thoracic and lumbar regions, the range of movement was between a quarter and a third of normal, and in the cervical region, rotation was about a quarter of normal, movements in other directions being much less restricted. Chest expansion was 6·25 cm.

The brachial pulse was absent in the left antecubital fossa, and a finely nodular cord was palpable at the usual site of the artery. Both radial pulses were of poor volume, and the femoral and ankle pulses were absent, but these vessels were not palpably thickened. Other pulses and vessels appeared normal. Oscillometry revealed greatly diminished pulsations in both thighs, and the flush of reactive hyperaemia was delayed in all the fingers and in the left thumb.

There was slight conjunctival pallor and a little cyanosis of the lips and nail beds. There was no atrophy of the skin or significant lymphadenopathy. The heart was clinically slightly enlarged to the left, and a soft apical systolic bruit was heard. There was neither venous engorgement nor oedema, and the lungs and abdomen showed no significant abnormality. The feet were pink and the toes warm and rather dry. Cutaneous sensation was impaired over the right forefoot and in the tips of the toes on the left, and vibration sense was also slightly impaired over the right great toe. Slight wasting of the muscles of the right thigh was present without notable weakness. No other abnormality of the nervous system was detected.

Radiographs of the hands (Fig. 2*b*) showed changes identical with those in Case 1, but more severe. The feet (Fig. 5*b*) showed similar but more extensive periarticular calcifications and slight porosis of the outer metatarsal heads. No calcification was visible in the metatarsal vessels. The knees (Fig. 4*b*) showed a little soft tissue calcification in the region of the femoral capsular attachments and severe arterial calcification, which continued in similar degree in the left anterior tibial artery as far as the ankle and in other calf vessels to a lesser extent. Faint calcification was visible in a tortuous right saphenous vein.

There was a little fluffy new bone on the outer aspects of both greater trochanters and anterior superior iliac spines (Fig. 6*b*), but the sacro-iliac and hip joints appeared normal. The pelvis showed a lesser degree of asymmetry of the type seen in Case 1. Heavy clumpy calcification was visible in the iliac, femoral, and profunda femoris arteries, which appeared widened, and in some of their larger branches.

The lumbar spine (Fig. 8*b*) appeared somewhat porotic with large disk impressions and small osteophytes on several vertebral bodies, but there was none of the bridging and gross ligamentous ossification seen in Case 1. The abdominal aorta was not calcified, but clumpy calcification was visible in two vessels in the upper abdomen, probably the left renal and gastro-duodenal arteries.

Calcified deposits were visible at the margins of most of the disk spaces in the thoracic region of the spine (Figs 9*b* and 10); in some situations these lay internal to osteophytes, and several of the deposits appeared to be unconnected with vertebral bodies. The appearances suggested that the deposits had occurred in the outer layers of the annulus fibrosus and there appeared to be a small deposit also in the substance of the T8/9 disk. The heavy calcifications lateral to the spine in Fig. 10 were in costal cartilages and no abnormal calcification

Fig. 10.—Case 2, radiograph of thoracic spine, showing marginal disk calcifications. In the lowest space these are unconnected with vertebral bodies. The heavy calcifications lateral to the spine are in costal cartilages.

was visible in the lung fields. Faint spotty and linear calcifications were visible in the arch and upper part of the descending thoracic aorta.

In the neck, the hyoid bone, and thyroid and cricoid cartilages, and the anterior aspect of the lower trachea were calcified. The lower disk spaces were slightly narrowed, with spotty calcification, and there was osteophytosis of the lower vertebral bodies. Spotty calcification was also present in several vessels, probably arteries, in the front of the neck.

Radiographs taken 16 months previously showed that several of the calcifications about the finger joints had increased appreciably in size while others had decreased; there had been no definite change in the radiographic appearances of the feet or pelvic vessels.

Laboratory Investigations.

Blood sedimentation rate 12/200 mm. (Westergren); Haemoglobin 84 per cent. (12·4 g./100 ml.); Haematocrit 43 per cent.; Mean corpuscular haemoglobin concentration 29 per cent.; White cell count 4,700/c.mm.; Differential count normal.

Serum calcium 10·1 mg./100 ml.; Serum phosphorus 3·3 mg./100 ml.; Serum alkaline phosphatase 12 units/100 ml.; Serum uric acid 1·2 mg./100 ml.; Serum cholesterol 210 mg./100 ml.

Urine normal.

Other Members of the Same Family

As this was clearly a familial syndrome, the family history of these patients was investigated in some detail. The parents of Cases 1 and 2, who were first cousins (Fig. 11), had both died from cerebro-vascular accidents. The father was known to be hypertensive in his later years, and his only sister died from a stroke at the age of 48 years. None of the earlier generation appeared to have had any changes in the joints similar to those of Cases 1 and 2.

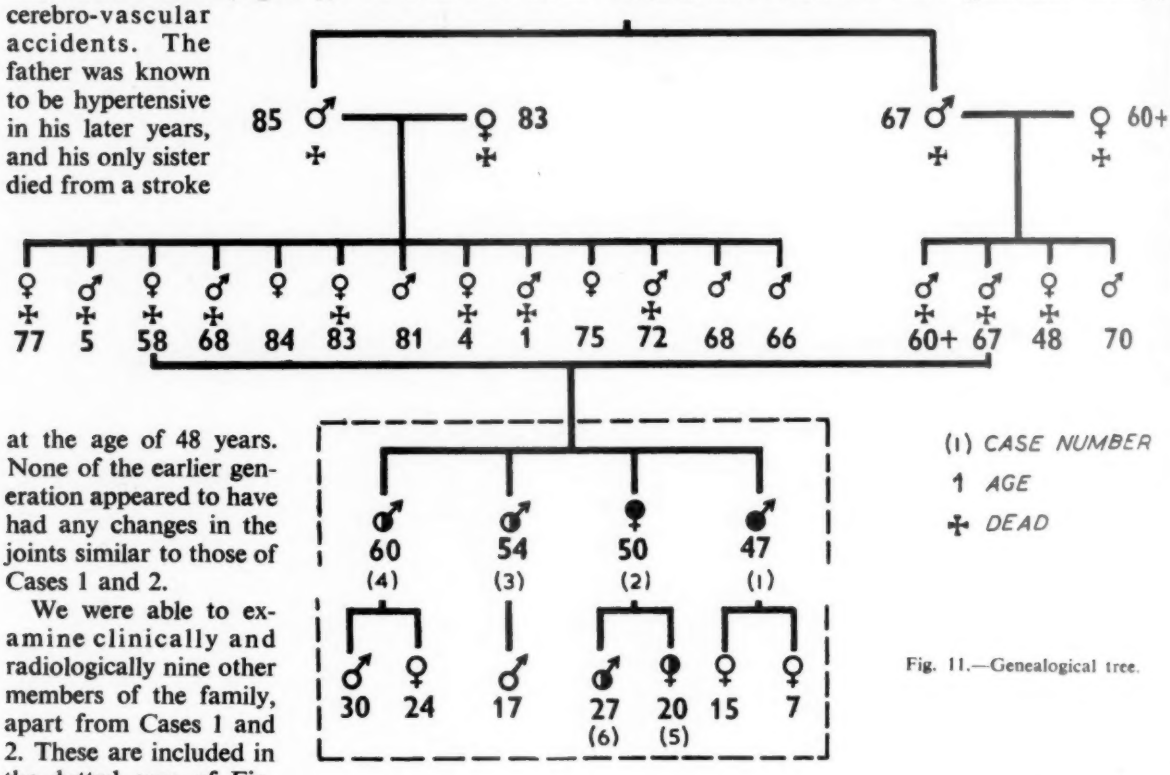

Fig. 11.—Genealogical tree.

We were able to examine clinically and radiologically nine other members of the family, apart from Cases 1 and 2. These are included in the dotted area of Fig. 11. Some manifestations of the familial disease were found in two brothers of the original patients, and in two children of Case 2. Brief records of these four cases are given below.

Case 3, the elder brother, aged 54 years, had always enjoyed good health.

Examination.—The only abnormalities noted were slight tortuosity and doubtful thickening of the right brachial, radial, and both posterior tibial arteries and mild hypertension. Radiographs disclosed no significant abnormality in the hands, feet, pelvis, or lumbar and cervical regions of the spine. Spotty calcification, much less dense than in Cases 1 and 2 was visible in the popliteal, posterior tibial, and proximal portions of the peroneal arteries on each side, and in the left first metatarsal artery.

Case 4, the eldest brother, aged 60 years, gave a history of recurrent attacks of low back pain since the age of 40 years and of angina of effort in the past 2 years.

Examination.—Severe hypertension and striking tortuosity and thickening of the right superficial temporal and right brachial and, to a lesser extent, of the left brachial and radial arteries were observed; the other limb vessels appeared normal. Moderate limitation of spinal movement and mild osteo-arthritic change in the peripheral joints were present. Radiographs of the hands, right forearm, feet, pelvis, lumbar and cervical spine, and chest showed evidence of disk degeneration and osteo-arthritis in the spine, and early osteo-arthritic change in the joints of the hands and feet. The heart was considerably enlarged. Faint spotty calcification was visible in the first and second metatarsal and right ulnar arteries.

Case 6, son of Case 2, now aged 27 years, gave a a history of symmetrical claudication in the calves on rapid walking since the age of 16 years. No abnormality was noted on physical examination. Oscillometry revealed diminished pulsations in the left calf. The radiographic appearances of the hands, feet, and cervical spine were normal. The pelvis showed the same type of asymmetry as Cases 1 and 2, and there was a slight compensatory lumbar scoliosis. Faint calcification was visible in both short saphenous veins; these were not tortuous or varicose.

Case 6, son of Case 2, now aged 27 years, gave a suggestive but not definite history of intermittent claudication in the calves on severe effort, also starting at the age of 16 years. No abnormality was noted on physical examination, or in the radiographs of the hands, feet, calves, pelvis, or lumbar and cervical spine. Oscillometry of the calves gave normal readings.

The five other members of the family who were examined were symptom free and appeared normal on examination. All were normotensive and showed negative results in the serum differential agglutination test. None had calcification of joint structures or of blood vessels in the hands, feet, pelvis, lumbar or cervical spine, or calves, but both the daughters of Case 1 and the daughter of Case 4 showed pelvic asymmetry of the type seen in Cases 1 and 2.

Mode of Inheritance.—The most probable mode of inheritance is by a rare recessive gene, Cases 1 and 2 being homozygous and presenting the full syndrome, and Cases 3-6 being heterozygous and developing the syndrome in an incomplete form. On this hypothesis, the children of Case 1 should also be heterozygous and should develop the incomplete syndrome in due course, and some of the children of Cases 3 and 4 may also be heterozygous. The occurrence of the pelvic asymmetry in children who are otherwise at present unaffected may be significant in this respect.

It is possible that forebears other than the parents of Cases 1 to 4 may also have been heterozygous and that the incomplete syndrome may sometimes cause little if any disability and be compatible with longevity.

Discussion

The main features of these six cases and of the two previously reported are summarized in the Table. The full syndrome affecting joints, juxta-articular bone, periosteum, and blood vessels as manifested in Cases 1 and 2 is a distinctive clinical picture. The history is usually characteristic, and the irregular, apparently largely bony, enlargement of joints, particularly of the fingers, and the nodular thickening of the peripheral arteries are striking. Radiologically, the changes in the joints and larger arteries are unmistakable. The spinal appearances in Case 1 in some views suggest ankylosing spondylitis, but it is quite exceptional to see such a degree of spinal change in ankylosing spondylitis without complete fusion of the sacro-iliac joints and squaring of lumbar vertebral bodies; the appearance of duplication of the lumbar vertebral plates is most unusual. Furthermore, the appearances in the thoracic spine of Case 2, which might reasonably be supposed to represent an earlier stage of this change, bear no resemblance to those of ankylosing spondy-

TABLE

SIX CASES COMPARED WITH THOSE PREVIOUSLY REPORTED.

Series			Magnus-Levy (1914)	Levitin (1945)	Present Investigations					
					Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age			47	24	47	50	54	60	20	27
Sex			F	M	M	F	M	M	F	M
Consanguinity			—	—	+	+	+	+	+	+
Sibs Affected			—	?+	+	+	+	+	?+	+
Descendants Affected			?+		—	+	—	—		
Claudication			+	—	+	+	0	0	+	?+
Radiologically Calcified Vessels	Limbs	Arteries	+	+	+	+	+	+	—	—
		Veins	—	—	+	+	—	—	+	—
	Visceral Arteries		+	+	?+	+	—	—	—	—
	Aorta		—	+	+	+	—	—	—	—
	Pulmonary Vessels		—	—	—	—	—	—	—	—
Blood Pressure (mm. Hg)			"200"	160/110	115/85	180/100	170/105	235/125	120/70	140/80
Joints Involved	Limbs		+	+	+	+	—	—	—	—
	Spine		—	—	+	+	—	—	—	—
Blood Chemistry				Normal	Raised alkaline phos-phatase	Normal				
Albuminuria			Trace	—	—	—				
D.A.T.					+	—	—	—	—	

litis, and the sacro-iliac joints are radiologically normal.

The change in severely affected arteries, as might be expected from the radiological appearances, appears to be of a distinctive type. Levitin (1945), who biopsied a posterior tibial artery in his patient, found the media and intima fibrosed and grossly distorted with bizarre calcified patches containing deeply acidophilic hyaline bodies or granules usually embedded in the calcified plaques which projected into a considerably narrowed lumen. Occasional smaller deposits were also present in the adventitia. This patient was the only one of the four showing the full syndrome who was without intermittent claudication, in spite of heavy calcification of all the main arteries of his lower limbs.

Calcification of the arteries and around the joints but sparing the viscera, the common site of metastatic calcification, has been described in association with advanced renal failure (Albright and others, 1937; Hubbard and Wentworth, 1921), but both these cases showed evidence of hyperparathyroidism and grossly abnormal biochemical findings in the blood, and neither showed any overgrowth of bone. None of the three patients with this syndrome so investigated showed evidence of metabolic disturbances of this kind, which implies that the calcification is of the dystrophic variety, that is, secondary to a primary disturbance in the tissues.

The syndrome can be distinguished both by its natural history and by the anatomical location of the deposits from the other well-recognized forms of dystrophic calcification divided by Steinitz (1931), on clinical grounds, into the two categories of calcinosis universalis and calcinosis circumscripta. The former occurs most frequently in children, and extensive calcium deposition is found in the skin, subcutaneous tissues, muscles, fasciae, and tendons, usually associated with the development of joint contractures and ulceration of the superficial deposits. Its prognosis is grave, the patient usually succumbing to intercurrent infection after a prolonged enfeebling illness (Brooks, 1934), although remission and recovery do occasionally occur (Weber, 1914; Kennedy, 1932; Craig and Lyall, 1931). In calcinosis circumscripta, mainly a disease of adult women, deposits occur most commonly in the skin and subcutaneous tissues of the upper limbs, especially of the fingers, but without particular relation to joints; it is commonly associated with reduced circulation in the extremities and sclerotic changes in the fingers.

Localized calcifications of tendino-capsular structures around joints, particularly the shoulder joint, are occasionally encountered; similar deposits have been noted less frequently at other sites, such as the wrist and finger joints, and sometimes at several sites in the same patient (Maseritz, 1935; Sutro and Cohen, 1941; Cooper, 1942; Vasko, 1946; Seidenstein, 1950). Hamilton (1951) suggested the descriptive title calcinosis localisata for this condition; the deposits may be asymptomatic, but are often revealed in radiographs taken to investigate acute painful swelling of the affected parts, the radiographic appearances resembling a minor form of the joint changes seen in the patients described above. In calcinosis localisata, however, the deposits frequently disappear after these acute episodes; this disease seems to have no familial incidence nor does vascular calcification occur in association with it.

Conclusion

The familial syndrome of calcinosis of the joints and arteries here described is remarkable in that the calcinosis is associated with periosteal bone proliferation and ossification of ligaments. It is therefore best regarded as a distinct entity until the mechanisms of dystrophic calcification are more fully understood.

Dystrophic calcification is probably due to a specific change in connective tissues, but it is not clear which connective tissue elements are concerned, and the nature of the disturbance is unknown. Future studies on the tissues of these patients may help to elucidate the problems of the site and mechanism of abnormal calcification and ossification in connective tissue.

Summary

In a family resulting from the marriage of first cousins, two of the four siblings display calcification of joint structures and arteries of an unusual type together with juxta-articular and periosteal new bone formation.

The son and daughter of one of these and the remaining two siblings appear to have a milder form of the syndrome affecting the blood vessels only.

The disease appears to be a rare and distinct heredo-familial form of dystrophic calcification.

I am greatly indebted to Professor J. H. Kellgren for much helpful advice, to Dr. H. Harris for assistance in the interpretation of the genetics of the syndrome, and to Dr. Robert Ollerenshaw and the staff of the Department of Medical Illustration for reproduction of the figures.

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Calcification vasculaire et articulaire hérédo-familiale

RÉSUMÉ

Dans une famille de quatre enfants née de l'union de cousins germains, deux d'entre eux sont atteints de calcification des structures articulaires et artérielles d'un type rare, associée à la néoformation osseuse, juxta-articulaire et périostique.

Les deux autres, ainsi que le fils et la fille de l'un des plus gravement atteints, semblent présenter une forme plus benigne de ce syndrome car chez eux l'atteinte ne porte que sur les vaisseaux sanguins.

Il s'agit ici probablement d'une forme hérédo-familiale rare et distincte de calcification dystrophique.

Calcificación vascular y articular heredo-familiar

SUMARIO

Dos de los cuatro hijos, frutos de la union de primos hermanos, presentan una calcificación de estructuras articulares y arteriales de un tipo raro, asociada con neoformación ósea, yuxta-articular y perióstea.

Los dos demás, así como un hijo y una hija de uno de los precitados parecen sufrir de una forma más benigna de este síndroma, que en ellos afecta sólo los vasos sanguíneos.

Se trata sin duda de una forma heredo-familiar, rara y distinta, de calcificación distrófica.

HISTOCHEMICAL STUDIES OF RHEUMATIC CONDITIONS

II. THE NODULE OF RHEUMATOID ARTHRITIS

BY

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(RECEIVED FOR PUBLICATION JANUARY 20, 1954)

Previous work on the present lines has been carried out by Glynn and Loewi (1952) on the nodule associated with rheumatic carditis. It is desirable to emphasize that the nodules of rheumatoid arthritis, although similar, are not the same, and that the actual enzyme preparations used were different; so that any differences between the results reported by these workers and those reported here do not necessarily imply a conflict between their findings and ours. Further, our findings are not necessarily applicable to fibrinoid changes described in many situations in other diseases.

Material and Methods

The nodules were excised under local anaesthesia and sectioned either immediately or after a few days' storage in a container at −40 C. Part of the nodule was fixed in 70 per cent. ethanol and cut after paraffin embedding; the remainder was cut on the freezing microtome without fixation to avoid artefacts of fixation. Unstained sections were examined by phase-contrast and polarized light, with repeated photographs to follow the progress of digestion. The staining methods employed were:

(1) Iron haematoxylin and Van Gieson's stain for collagen.

(2) Periodic acid—Schiff (P.A.S.) for mucopolysaccharide (Hotchkiss, 1948); control sections were acted on with diastase and lipoid solvents to exclude false positive results from glycogen and lipoids.

(3) Laidlaw's silver impregnation for reticulin to show argyrophilia.

(4) Mallory's phosphotungstic acid—haematoxylin (P.T.A.H.) which stains collagen a reddish-brown and fibrin and fibrin-like substances a dark blue.

The enzyme preparations used were those described in our previous paper (Fawns and Landells, 1953), with the addition of a standard commercial preparation of pepsin (Light). Because of the expense of the collagenase and the frailty of the sections, incubation was usually carried out on slides under coverslips with a paraffin-vaseline seal. The duration and concentrations employed were:

Collagenase, trypsin, pepsin—1 mg./ml. at 37° C., ¼ to 20 hrs.

Hyalase (Benger)—1 ampoule/ml. at 37° C., 2 to 48 hrs.

The specificity of the enzymes has been reported in our previous paper, but the efficiency and specificity of collagenase have since been called into question by Pearse (1953), though he gives no details of the experiments. It is true that its action is slow, and for dense material like adult human tendon exceedingly slow, but dermal collagen, taken as a control for these experiments from the knee or elbow, and the collagen of decalcified bone are reliably dissolved in some 15-30 hours, using a pure concentrated preparation. A suspension of rat-tail collagen (10 ml.), made by the method of Nageotte and Guyon (1931), and incubated at 37 C. with 5 ml. of our collagenase solution, was completely digested to a water-clear solution in about 1 hour and 50 minutes, whereas control suspensions incubated with trypsin were unchanged after overnight incubation. Elastic fibres, keratin, fibrin, and all the other proteins tried, except gelatin, were untouched by collagenase. It will not act after formalin fixation, though it will act after alcohol fixation, but at a slower rate. No hyaluronidase activity was observed with the samples of collagenase used.

Structure of the Nodule

Although the studies of Collins (1937, 1939, 1949) make it unnecessary to go into great detail, it is desirable to outline the topography of the nodule so that no doubt remains as to the meaning of the descriptive terms used. As seen clinically, nodules mostly measure from 5 to 40 mm. across, and are rounded, painless, and mobile. The cut surface of the smaller nodules shows a soft, yellow, central core, surrounded by a firm, hyaline, fibrous zone which merges indefinitely with the looser normal collagen of the dermis around. The larger nodules are formed by an agglomeration of similar areas.

Histological sections (Fig. 1, opposite) show this softened central core as an area of structureless material giving the staining reactions of fibrin, amongst which some bundles of collagen can usually be identified; there are no living cells in this area, though there may be nuclear debris, features which have given rise to the rather loose term "fibrinoid necrosis of collagen". Outside this,

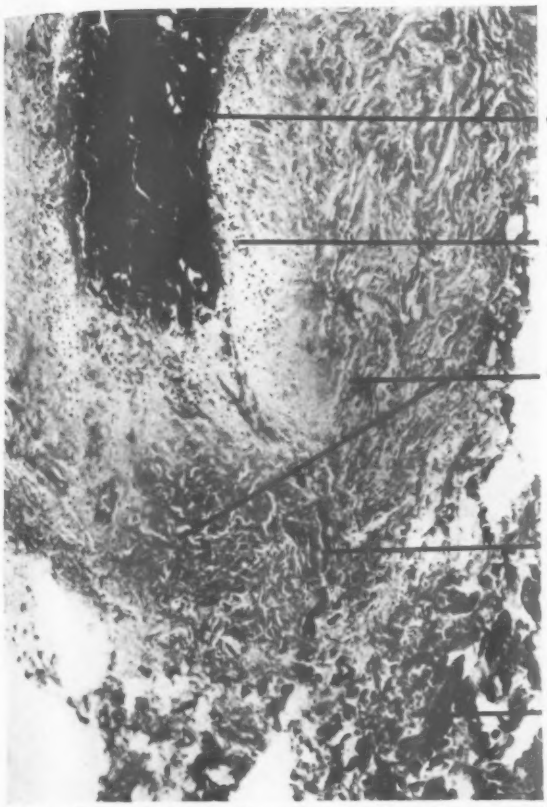

Fig. 1.—Zones of rheumatoid nodule. Paraffin section; phosphotungstic acid—haematoxylin; × 64.
(*a*) fibrinoid core with faint collagen strands;
(*b*) corona cells;
(*c*) compact zone, paler and with different architecture;
(*d*) one strand dermal collagen passing along axis of nodule through compact zone to break up in fibrinoid zone;
(*e*) dermal collagen in darker looser bundles.

there may be found a cellular zone, with large and sometimes multinucleate cells resembling fibroblasts or histiocytes arranged as a palisade around the core; among these are radially arranged collagen and reticulin fibres. Collins' term "corona" is a convenient brief title for these cells. They lie between the fibrinoid centre, and the encircling zone of compact fibrous tissue; some of them are found among the fibres of this zone. The periphery of the nodule merges with the loose original collagen of the dermis. The P.T.A.H. stain used for the photograph shows these points clearly and emphasizes the difference between the collagen of the compact zone and of the dermis. There are variations in detail in individual nodules and around the circumference of any single necrotic focus, which we believe to be due to the age changes going on in nodules in the living body.

Results

In the fresh section, the soft centre of the nodule can be seen to consist of two distinct elements: one fibrillar, the other granular (Fig. 2). In fixed sections, the granular material may appear either fibrillar or plastered up on the surface of the collagen fibres, and it is often difficult to distinguish the two elements. Bulk chemical analyses of fibrinoid will inevitably fail to separate the two elements and may include some of the surrounding collagen. There appears to be a place, therefore, for histochemical techniques with selective removal of the two components by specific enzymes followed by appropriate staining. The two elements can be separated; the enzyme collagenase dissolves the fibrillar material but not the granular, and trypsin dissolves the granular but not the fibrillar. The fibrillar material is traceable into the bundles of

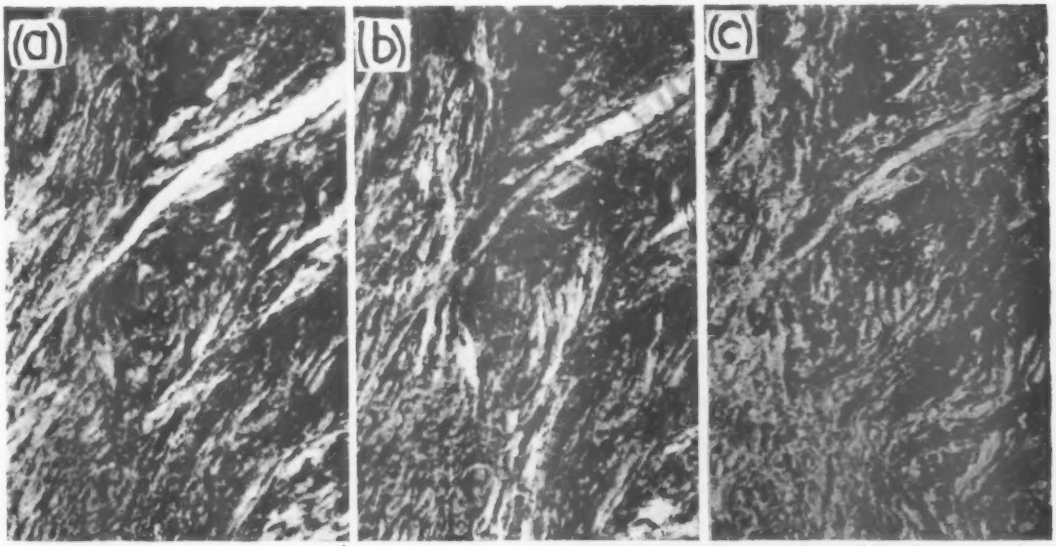

Fig. 2.—Action of collagenase. Fresh frozen sections; unstained; photographed first by ordinary light, then by polarized light on same negative, which shows up collagen as bright fibres; × 125. (*a*) before digestion, (*b*) after 2 hrs, (*c*) after 4 hrs.

Fig. 3.—Argyrophilia and formation of nodule. Paraffin section; Laidlaw's reticulin stain; × 150.
Early argyrophil change without much fibrinoid. Some collagen fibres of large bundle are grey (normal), others, on surface, are black (A-collagen); some finer fibres on right are probably new reticulin fibres in corona.

Fig. 4.—Another field from same section as in Fig. 3; × 84.
More fibrinoid has accumulated, A-collagen is more broken up, corona cells are better seen, one being multinucleate. Transition of normal collagen bundle into A-collagen again well shown at bottom.

surrounding collagen, which it resembles in birefringence, but from which it differs in being argyrophil; it is not P.A.S. positive. The granular material has no normal counterpart, and is refractile but not birefringent; it is not argyrophil, but is strongly though variably P.A.S. positive.

Further consideration of the process of fibrinoid necrosis involves taking these components separately, and allowing for the secondary changes that take place in both materials in the history of the nodule. For brevity and simplicity, the granular material will be termed *fibrinoid*, and the argyrophil collagen will be termed *A-collagen*. The expression "fibrinoid necrosis" covers both the change of collagen into A-collagen and the accumulation around it of the fibrinoid.

(1) A-Collagen.—This material retains the enzyme susceptibility of the original collagen, *i.e.* it is dissolved by collagenase but not by trypsin. It is neither more nor less sensitive than normal collagen bundles of a similar size. It is not P.A.S.- or P.T.A.H.-positive as is the fibrinoid material. The important distinction between A-collagen and normal collagen appears to be the argyrophilia shown by the former. At no stage in the digestion of normal collagen by collagenase does argyrophilia develop, nor have we obtained it by the action of other enzymes on collagen. It is safer at present not to assume the identity of A-collagen and reticulin, especially as this is P.A.S.-positive: one is connected with collagen in formation, the other with collagen in the process of destruction.

The expression "argyrophilia", applied to collagen or reticulin, is a simple term for a complex histological reaction. It implies that the fibres will accept, after an essential preliminary series of washings known as the Mallory bleach,* an incrustation of ammoniacal silver which can be reduced *in situ* to metallic silver by substances such as formaldehyde. Argyrophilia appears (Figs 3 and 4) to be asso-

* Mallory bleach: 5 minutes each in Lugol's iodine, sodium thiosulphate 5 per cent., potassium permanganate 0·25 per cent., oxalic acid 5 per cent., with intermediate washings.

ciated with the break-up of larger bundles, which are non-argyrophil, except sometimes on the surface, but which are continuous with individual argyrophil fibres. These are at first elongated and sinuous (with sharper and wider curves than normal) but remain fibrillar. Eventually this material breaks up into smaller fragments and disappears, but the argyrophil change precedes this solution, and it is therefore unlikely that the argyrophilia relates to the amino-acid protofibril chain, since if this were deranged it would presumably result in the loss of fibrillar structure. It is therefore likely to be concerned either with the ground substance or with the side-chains.

(2) **Fibrinoid.**—This is present in fresh material as granular droplets of varying size, refractile but not birefringent. It is not argyrophil as above defined. It always stains orange to yellow with Van Gieson's stain, and is strongly P.A.S.-positive. In many, but not all areas, it stains dark bluish-black with P.T.A.H.; with ordinary haematoxylin and eosin it is bright red. These staining reactions, resembling those of fibrin, are responsible for the name. But recent biophysical studies by Kellgren and others (1951), and chemical analysis by Consden and others (1952), both strongly indicate that there is no fibrin, at any rate not in amounts sufficient to account for the bulk of material present.

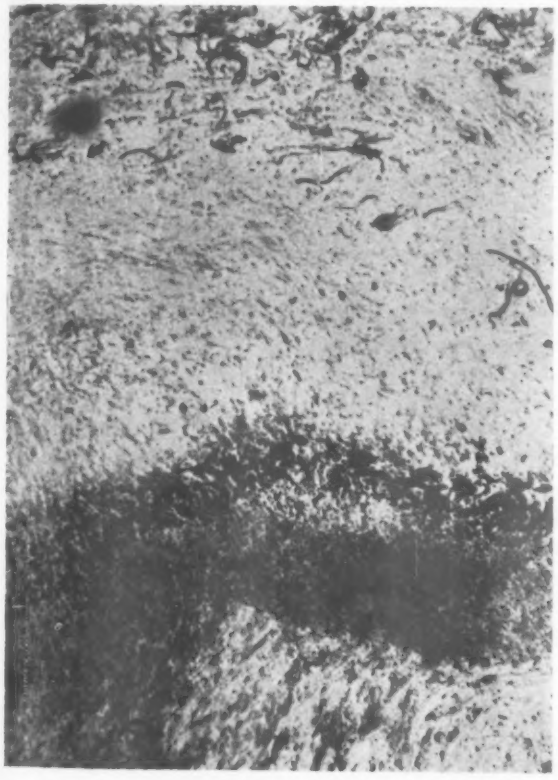

Fig. 5.—Action of collagenase, and two sizes of fibrinoid granules. Technique as in Fig. 2; fresh unstained frozen sections; × 95. Collagenase action for 20 hrs. Bright collagen fibres absent, but elastic fibres of the subcutis undigested; elastic fibres almost absent from compact zone and fibrinoid. Two sizes of fibrinoid granule, with a sharp straight border above the large granular material, in position of corona cells.

The results of enzyme action on fibrinoid are quite different from the results on collagen. Fibrinoid is rapidly dissolved by trypsin, but is in any case appreciably soluble in water before fixation. It is not digested by hyalase, although the strong P.A.S. reaction suggests the presence of polysaccharide, nor is it metachromatic, differing in both points from the mucopolysaccharide of the normal ground substance of connective tissue. There are three possibilities which are not mutually exclusive:

(*i*) the chemical structure of this polysaccharide is not that of normal ground substance,
(*ii*) the polysaccharide is combined with protein in such a way that the reactive groups are blocked,
(*iii*) it may be attacked, but the cleavage products remain attached to protein and do not diffuse away.

The fibrinoid granules appear to be of two sizes, visible in the fresh section, but particularly conspicuous where the collagen has been removed by collagenase (Fig. 5). The smaller granules stain less strongly with P.A.S. and P.T.A.H., and are readily digested by both trypsin and pepsin; the larger, strongly P.A.S.- and P.T.A.H.-positive, are slowly digested by trypsin and withstand digestion by pepsin at a time when both collagen and the small granules have been completely removed (Figs 6 and 7, overleaf). This large granular material tends to lie near the corona cells.

Discussion

(1) **Changes in Collagen.**—Our observations suggest that the alteration of collagen takes place in the side-chains, since the A-collagen is still fibrillar, and argyrophilia cannot be demonstrated until the surface has been treated with agents, like the Mallory bleach or periodic-acid, which can be thought of as acting on the ground substance. Preliminary tests with blocking techniques suggest that the basic amino-acids, arginine and histidine, are concerned; this is in keeping with the chemical facts that they have the necessary groups to combine with acidic ground-substances. Their structure admits the possibility of the acceptance of silver, and argyrophilia has already been linked to histidine

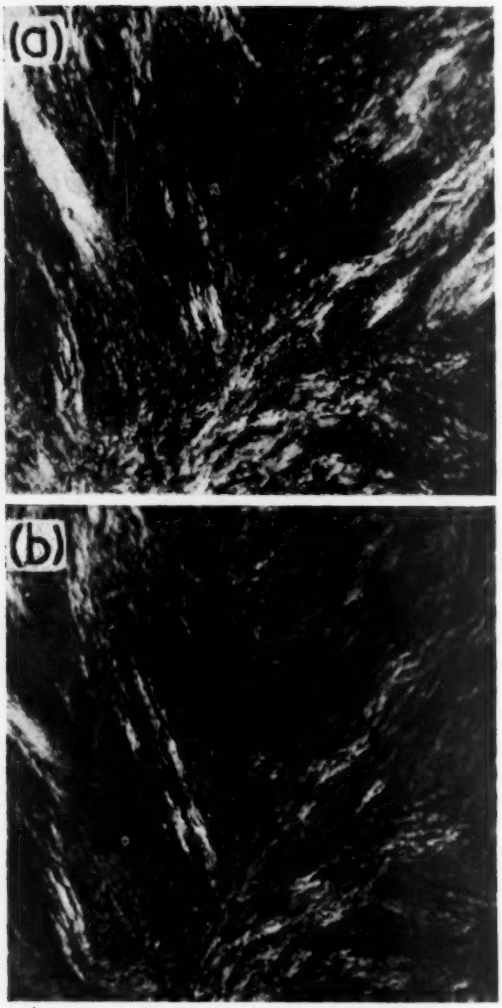

Fig. 6.—Action of hyalase and trypsin. Technique as in Fig. 2; fresh unstained frozen sections; × 125.
(*a*) before and after hyalase—appearance unchanged acting as a control for (*b*) consecutive section digested for 4 hrs with trypsin. Dark fibrinoid material removed.

by the observations of Peters (1953). At the moment this is as far as our results will take us.

(2) Changes in Fibrinoid.—Only two histochemical reactions of this substance can be said to be firmly established: the strong P.A.S. reaction, indicating polysaccharide, under the conditions in which we have carried it out, and a strong reaction for tyrosine, demonstrated histochemically by Millon's reagent and chemically by Consden and others (1952). These are not observed with normal connective tissue; the quantity in which fibrinoid is found and these chemical differences make it improbable that fibrinoid results from a pathological change in the pre-existing material without the incorporation of adventitious material, which, for

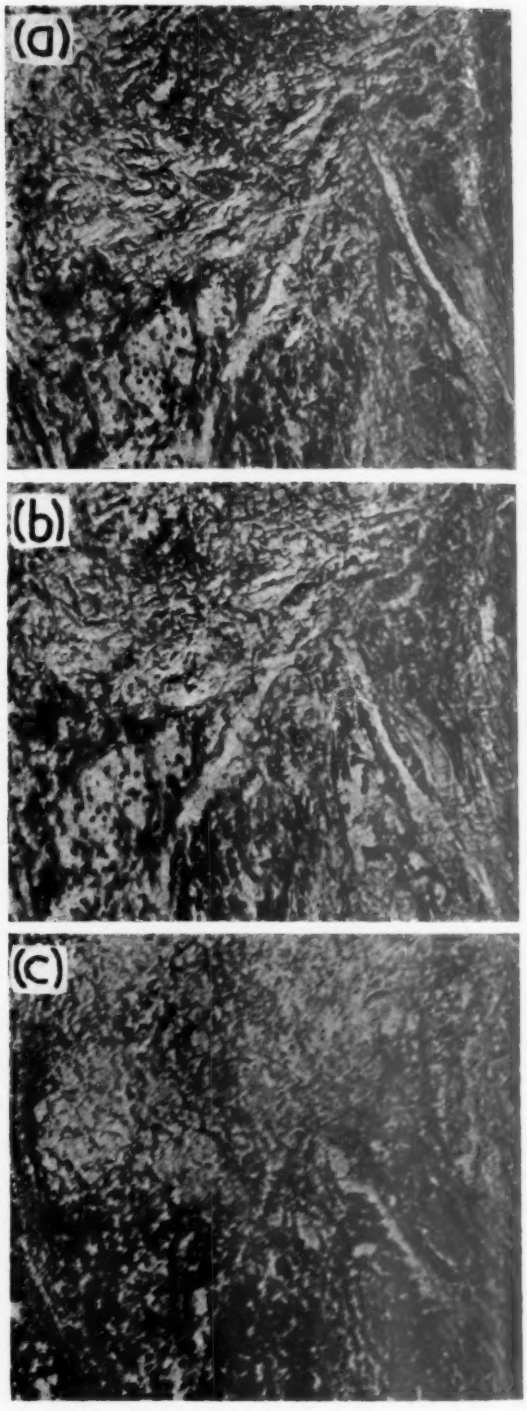

Fig. 7.—Action of pepsin. Technique as in Fig. 2; fresh unstained frozen sections; × 125.
(*a*) before incubation,
(*b*) after 2 hrs,
(*c*) after 4 hrs.
Large granular material still present; collagen and small granules removed.

the reasons given, is probably not fibrin. A substance new in components and considerable in quantity is more likely to represent a synthesis resulting from cellular activity than a passive degradation or accumulation of material. This synthesis could take place elsewhere in the body, and the product be deposited in the nodule, but it would be reasonable to credit the deposition to the local corona cells which often contain droplets of P.A.S.-positive material.

The coarsely granular, P.T.A.H.-positive fibrinoid is found in two places:

(*i*) as a sharply limited deposit in close relation to, but always internal to, the corona cells,

(*ii*) as an infiltrating deposit among fibres in parts of the nodule where the corona is lacking.

This second location must imply either that the rheumatoid degenerative process travels along the fibres, with fibrinoid being liberated from the fibres without the action of any cells (which is not very probable), or that the material is mechanically displaced (which is very likely to happen with a semi-fluid substance in the living body, with every movement). The fact that fibrinoid is sometimes found away from the corona is therefore not an insuperable objective to a suggestion that it is formed by the corona cells.

It would appear that the coarsely granular fibrinoid is the original form, and that the smaller granules (which are P.T.A.H.-negative, though still P.A.S.-positive) represent the first step in its degeneration. Later it becomes thinner and vacuolated, and occasionally other steps in its digestion are suggested by the metachromasia and basophilia which is seen regularly where phagocytes are present. The histological changes are much more easily explained by this sequence than by the reverse, or than by the supposition that a number of different sorts of fibrinoid are formed.

(3) **Pathogenesis of the Nodule.**—In the nodule shown in Fig. 1 the formation of zones is clearly seen around the dark bundle of fibres, and is traceable into the loosely-meshed collagen of the subcutis, like which it stains. This bundle passes right through the paler but more densely packed collagen of the compact zone and into the central area of fibrinoid necrosis, where it becomes broken up and argyrophil. It is hard to believe that this bundle, which is clearly formed of original collagen, and which lies in the axis of symmetry of the nodule, could be unrelated to the cause of the nodule, having merely been incorporated by chance into a degenerative process starting in some unexplained mass of new collagen. From the examination of many areas, it would appear that the order of events is as follows: firstly, the argyrophil change, then the arrival of corona cells, and then the formation of the fibrinoid and the surrounding compact zone in roughly corresponding quantities (Figs 3 and 4). Subsequent changes lead to the breakdown and absorption (often incomplete) of the fibrinoid. The corona cells which form a physical barrier to the displacement of the fibrinoid, may be concerned in its formation or solution, but the presence among them of reticulin and collagen fibres makes it reasonable to credit them with the formation of the compact zone; their position inside it would be hard to reach if they had not themselves laid it down from the inside.

These observations suggest that the rheumatoid process consists partly in a change in the collagen and partly in the failure of an active process of repair. When, as happens here, the process results in the formation of a mass of new tissue, it would appear more reasonable to think of it thus than as the primary degeneration in a static material, which is implied in the term "fibrinoid necrosis". The chemical site of this failure is still not clear, but the point to which our tentative observations direct attention is the facet where argyrophilia, collagenase action, and polysaccharide attachment appear to meet, namely, that relatively small part of the collagen amino-acid chain made up of the amino-acids arginine and histidine.

Summary

(1) The central soft area in the rheumatoid nodule consists of two elements:

(*a*) collagen fibres that have undergone a change which begins by rendering them argyrophil and ends in their destruction;

(*b*) a granular substance (fibrinoid) that is always strongly P.A.S.-positive and may show other staining reactions similar to those of fibrin.

(2) These two components are separable by enzyme action: collagen is removed by collagenase and the granular material by trypsin. This granular material appears in two forms: large granules resistant to pepsin, and small granules digested by pepsin. The larger granules are P.T.A.H.-positive and are probably the first to appear.

(3) Secondary changes in the course of the evolution of the nodule account for variations in its composition and therefore in its staining reactions.

(4) Active cellular synthetic processes as well as degenerative and necrotizing processes are necessary for the formation of the nodule.

We should like to thank Miss R. M. Jenkins and Mr. V. Trenwith for technical, and Mr. A. J. King and Mr. A. Gallup for photographic assistance. The nodules were obtained through the kindness of Dr. W. S. Tegner

and Dr. J. W. T. Patterson. The Yarrow Research Fund of the London Hospital made a grant towards expenses.

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Étude biochimique des affections rhumatismales
II. Le nodule de l'arthrite rhumatismale

RÉSUMÉ

(1) La partie centrale molle du nodule rhumatismal consiste de deux éléments:

(*a*) des fibres collagènes qui ont subi des altérations commençant par l'argyrophilie et aboutissant à leur destruction;

(*b*) une substance granulaire (fibrineuse) prenant toujours fortement le acide-périodique-Schiff et capable de prendre d'autres colorants de la fibrine.

(2) Ces deux composants peuvent être séparés par l'intervention d'un enzyme: le collagène s'enlève par la collagénase et la substance granulaire par la trypsine. Cette substance granulaire se présente sous deux formes: de grands granules, résistants à la pepsine et de petits, digérés par elle. Les plus grands granules sont acide-phosphotungstique hematoxyline-positifs et se présentent probablement les premiers.

(3) Des altérations secondaires au cours de l'évolution du nodule expliquent les variations de sa composition et par conséquent de ses réactions de coloration.

(4) Un processus cellulaire actif de synthèse autant que de dégénérescence et de nécrose est nécessaire à la formation du nodule.

Estudio bioquímico de las afecciones reumáticas
II. El nódulo de la artritis reumatoide

SUMARIO

(1) La parte central blanda del nódulo reumático consiste de dos elementos:

(*a*) fibras colagenas que han sufrido alteraciones comenzando con argirofilia y acabando en su destrucción;

(*b*) una substancia granular (fibrinosa) siempre fuertemente acido-periodico-Schiff-positiva y capaz de otras reacciones de coloración, como la fibrina.

(2) Estos dos componentes pueden separarse por la acción enzimática: el colageno se elimina por la colagenasa y la substancia granular por la tripsina. Esta substancia granular aparece en dos formas: gránulos mayores que resisten a la pepsina y menores, digeridos por ella. Los gránulos mayores son ácido-phosphotungstico-hematoxilino-positivos y aparecen probablemente primeros.

(3) Alteraciones secundarias en el curso de la evolución del nódulo explican las variaciones de su composición y, por consiguiente, sus reacciones de coloración.

(4) Un proceso celular activo de síntesis así como él de degeneración y de necrosis es necesario para formar el nódulo.

HISTOPATHOLOGICAL CHANGES IN SARCOLEMMA AND SARCOPLASM IN COXSACKIE VIRUS INFECTION

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(RECEIVED FOR PUBLICATION DECEMBER 7, 1954)

Between 1948 and 1950, Dalldorf and Sickles (1948), Dalldorf and others (1949), Dalldorf (1950), and Sickles and Dalldorf (1949) reported a previously unidentified virus in the faeces of children with the symptoms of acute anterior poliomyelitis. This virus has been named Coxsackie or C.-virus, and many authors (Magnus, 1949; Kaplan and Melnick, 1951; Melnick, 1947, 1950a, 1950b; Melnick and Godman, 1952; Melnick and Horstmann, 1947; Melnick and Kraft, 1950; Melnick and Ledinko, 1950; Melnick and various others, 1949, 1950a, 1950b) have contributed towards the elucidation of its epidemiology and serology. Moreover, in acute anterior poliomyelitis the virus could be shown in Bornholm disease (myalgia epidemica; Sylvest, 1933) and in certain forms of gastroenteritis.

Two reports on the symptomatology of pure Coxsackie virus infection appeared in 1950. Shaw and others (1950) described a laboratory infection in six assistants engaged on the isolation of C.-virus. The symptoms were raised temperature, feeling of general weakness, lack of appetite, pains in the throat, single instances with stiffness of the neck, and in some cases diarrhoea, and 2 days later pains localized in the muscles of the abdomen, thorax, and extremities. Hueber and others (1951) reported the appearance of an epidemic C.-virus infection. The C.-virus has since been isolated during epidemics in Switzerland (Thelin and Wirth, 1951), and during a typical outbreak of Bornholm disease in England and Scotland (Brown, Liddle, and Tobin, 1952; Davies and Warin, 1951).

Up till now, fourteen antigenically different strains of varying toxicity and tissue affinity have been isolated. One strain (Texas) has shown a decided affinity for the striated skeletal musculature and for the connective tissue.

The histopathological changes in the muscles during a C.-virus infection in mice were shortly described by Strandberg (1952) and were later reported by Godman and others (1952).

The present investigations have been carried out to ascertain whether the histopathological changes in the muscles in C.-virus infection are comparable with the muscular dystrophies of central origin (poliomyelitis, sclerosis lateralis amyotrophica, etc.) or with the genuine muscular dystrophies (polymyositis, dermatomyositis, dystrophia musculorum progressiva, etc.).

Experiments

In the State Serum Institute, Magnus carried out experiments with the C.-virus (Texas strain) administered to 188 albino mice in titres varying between 10^{-1} and 10^{-8}. The mice were grouped according to age: 1, 5, 10, 14, 18, and 21 days. Inoculations were given intraperitoneally in penicillin-streptomycin-saline solutions: 0·02 ml. to mice one day old, 0·03 ml. to all the others.

(1) 77 mice were inoculated during the first 5 days of life with virus titres varying between 10^{-1} and 10^{-8}; the primary mortality was 100 per cent., and 22 per cent. died before developing paralysis.

(2) 41 mice were inoculated on the 10th day of life; the primary mortality was 95 per cent., and four mice died before developing paralysis.

(3) 28 mice were inoculated on the 14th day of life. Mortality due to infection was 50 per cent. Fourteen of the mice were inoculated with virus titres varying from 10^{-1} to 10^{-2}, and ten died; the fourteen others were inoculated with virus titres varying between 10^{-3} and 10^{-4}, and only four died. All the mice in this group had paralysis of one or more extremities.

(4) 42 mice were inoculated on either the 18th or the 21st day of life. All survived the infection, but only 7 per cent. developed paralysis of one or more extremities.

As a result of these experiments, the following groups of test animals were used:

(*a*) 22 mice inoculated at 14 days old with a solution of C.-virus, the titres varying between 10^{-3} and 10^{-4}.

(*b*) Nineteen healthy controls.

Twelve of the infected mice were examined when 4 to 7 weeks old and the rest when 16 to 19 weeks old. All the infected animals had developed manifest paresis of one or both hind legs.

Series of sections of infected and healthy gastrocnemius muscle were prepared in the Psychiatric Laboratory, University of Copenhagen. The tissues were sectioned at about 5 μ, and the preparations were stained with haematoxylin and eosin.

A number of these preparations were de-stained and de-paraffined, and used for studying the structural changes by polarization microscopy at the Neurophysiological Institute, University of Copenhagen.

Results

Appearances in Controls.—All preparations of the gastrocnemius muscles of the nineteen healthy controls showed approximately identical features. Longitudinal sections revealed fairly uniform thickness of fibres. Eosinophilic staining of the sarcoplasm was uniform. The myofibrils were poorly visible. The nuclei were spindle-shaped, homogeneous in structure, and situated immediately inside the sarcolemma.

The sarcolemma was of uniform thickness, investing the intact muscle fibre. There was no entry of round cells, and no oedema.

The cross sections correspondingly showed fairly uniform fibre diameters, and peripherally situated nuclei, with the sarcolemma tightly enclosing each muscle fibre. Polarization microscopy of the striated structure revealed normal cross striation of all longitudinally sectioned fibres (Fig. 1*a*).

Variations in Cross Striation.—Pathological changes were ascertained in all preparations from the 22 mice inoculated with C.-virus. On one preparation the striation was normal and well-defined; in the remainder examined by polarization microscopy there was every variety of reduced definition of striation, until its complete disappearance (Fig. 1*b*). In some cases the character of the changes was diffuse, but in others the changed definition of striation was found within the individual fibres.

Variations in Muscle Fibre Diameters.—The preparations showed greater variation in the diameters of the muscle fibres in the C.-virus infected than in the controls (Fig. 2, opposite). The maximum fibre diameters were, therefore, measured (with the ocular micrometer) in 1,000 sections from ten healthy and ten infected mice. In the affected animals the diameters varied between 9 and 69 μ (standard deviation 12·4 μ; arithmetical mean value 33·2 μ; standard error 0·3 μ). In the healthy animals, the corresponding figures were 24 to 63 μ (standard deviation 7·1 μ; average: 38·5 $\mu \pm$ 0·2 μ).

The difference between the percentual distribution graphs shows that 43 per cent. of all measurements of preparations from animals infected with C.-virus were either higher or lower than those on preparations from healthy controls (Figs 3*a*, *b*). The average

Fig. 1(*a*).—Cross-striated fibres of gastrocnemius muscle from healthy albino mouse. Longitudinal section, polarization microscope, × 500.

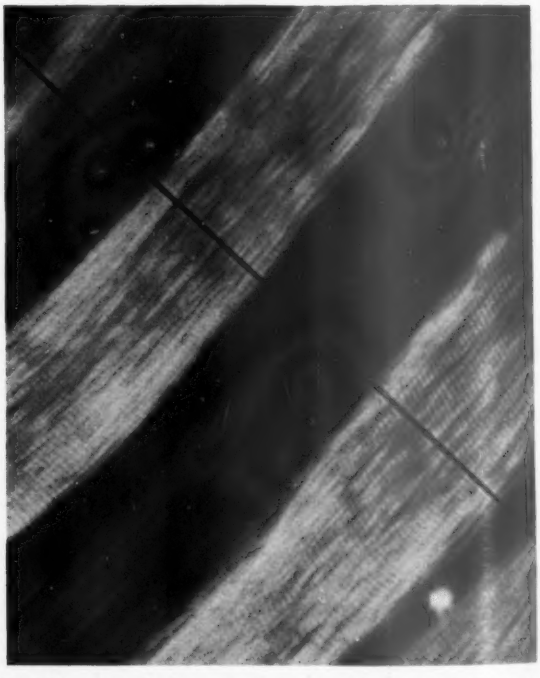

Fig. 1(*b*).—As 1(*a*) from C.-virus inoculated mouse. The cross striation is only faintly visible, and has completely disappeared in some places. × 500.

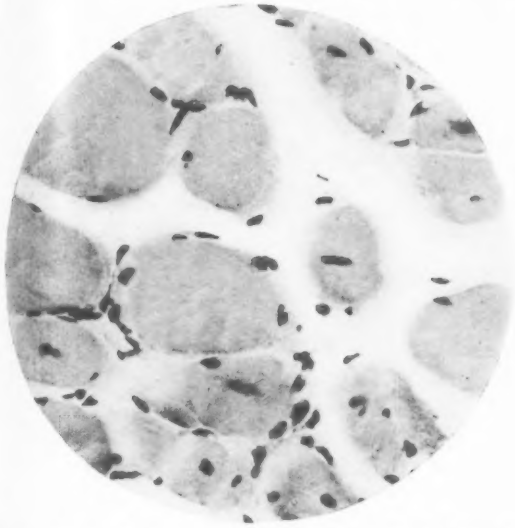

Fig. 2.—Fibres of gastrocnemius muscle from C.-virus inoculated mouse. Cross-section, × 400. Note variations in size of fibres.

area of muscle fibre (expressed in terms of average radius in μ) of 250 cross sections from ten infected and ten healthy mice revealed no difference between the two categories ($17{\cdot}5\,\mu$ and $17{\cdot}4\,\mu$ respectively), whereas the standard deviation was considerably increased in the infected animals ($1{\cdot}4\,\mu$) as compared with the healthy controls ($0{\cdot}9\,\mu$).

Histopathological Findings.

Preparations of Cross-Sections of Fibres from C.-virus-infected Mice.—The fibres were oval or roughly circular. Fibres of unusually small diameters were seen alongside and between large-diameter and apparently normal-diameter fibres. In no instance was there a tendency towards concentration in patches of these atrophic fibres. There was a noticeable increase in the number of fibres with diameters greater and smaller than normal, and the hypertrophy of the individual fibres was greater than in the controls. This mixture of hypertrophic and atrophic fibres leads to the assumption that the virus attacks peripherally and not through the central nervous system.

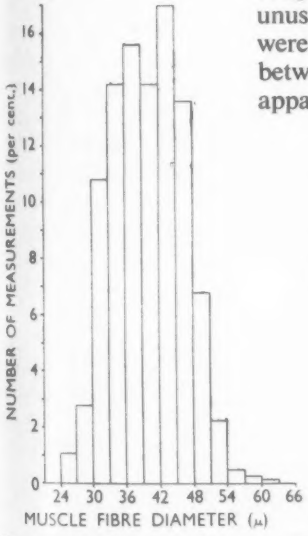

Fig. 3(*a*).—Differences in size of fibre diameters (in μ) from gastrocnemius muscle in a healthy control. (Standard deviation: 7·1 μ.)

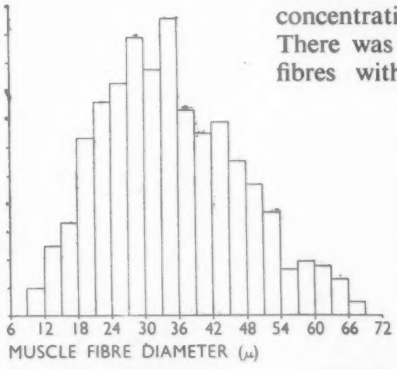

Fig. 3(*b*).—Differences in size of fibre diameters (in μ) from gastrocnemius muscle in C.-virus inoculated mouse. (Standard deviation: 12·4 μ.)

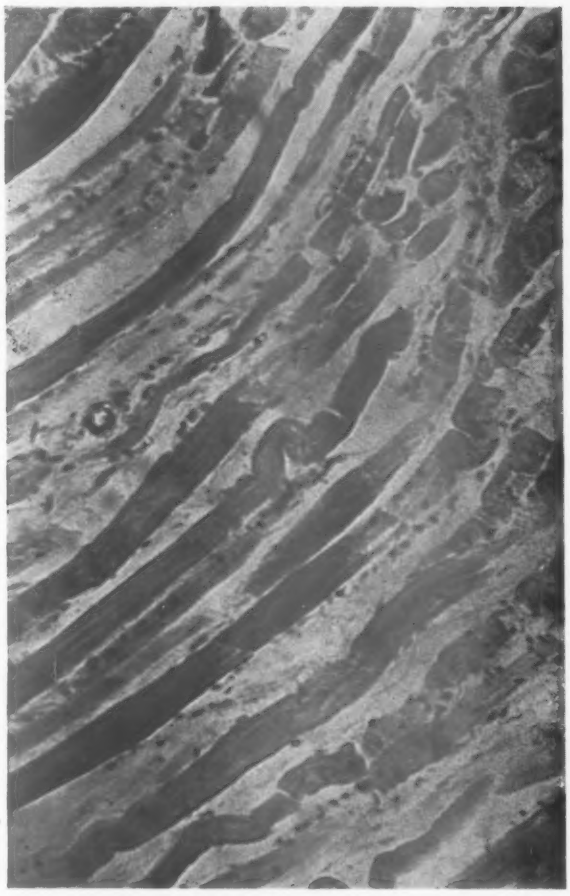

Fig. 4.—Longitudinal section of gastrocnemius muscle from C.-virus (Texas strain) inoculated mouse. Note deviation of some fibres from the normal longitudinal position with twisting and folding of the sarcoplasm; different fibres with different affinities to the stain, indicating the beginning of hyaline degeneration; slight perivascular and interstitial round cell infiltration; fragmentation of sarcoplasm within the sarcolemma sheath. × 100.

Changes in Position (Fig. 4).—In all preparations a varying number of muscle fibres deviated from their longitudinal position. They twisted round the longitudinal axis, and the

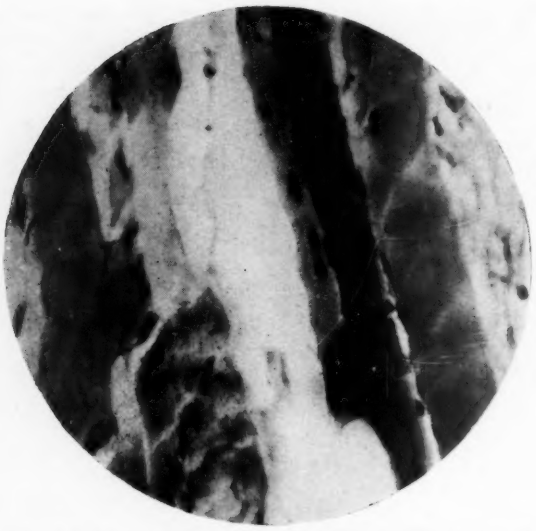

Fig. 5.—Longitudinal section of gastrocnemius muscle from C.-virus inoculated mouse. × 300. Hyaline degeneration of fibres in different stages.

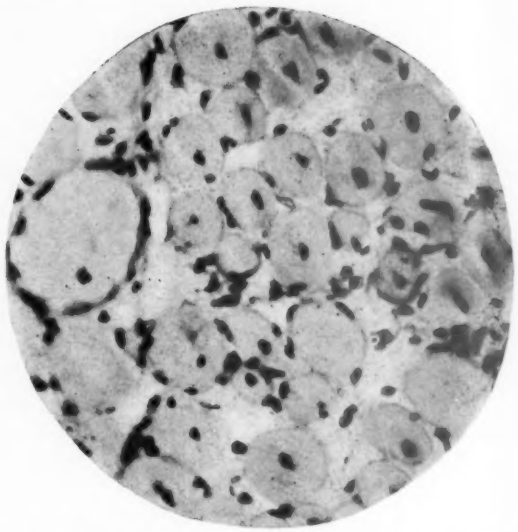

Fig. 6.—Cross-section of gastrocnemius muscle from C.-virus inoculated mouse. × 400. Note variation in size of muscle fibre diameters, nucleus in middle of fibre, sarcolemma sheath with varying thickness, and slight interstitial round-cell infiltration.

sarcoplasm was folded and twisted within the sarcolemma sheath. These folds tended to become isolated from the remaining sarcoplasm. The fragments sometimes consisted of normal sarcoplasm, but were formed in other instances from reticular or vacuolated sarcoplasm.

Longitudinal Division of Muscle Fibre into two or more smaller fibres was noticed in a number of preparations.

Concentric Division and Circular Formation did not occur.

Hyaline Degeneration.—Varying phases of hyaline degeneration to the point of calcification (Fig. 5) were observed in practically all the preparations and resembled the degenerations reported by Zenker. It either appeared along the whole length of the fibre or was confined to definite areas within the individual fibre. The hyaline portions appeared either fissural or fractured.

Calcification.—There was pronounced calcification in four preparations from infected mice.

Changes in Myofibrils.—In some preparations the basophilic staining of the fibrils was above standard, and in others the structure was more or less blurred, and the well-defined myofibrils were situated like tight, thick, parallel, frequently wavy, lines along the whole length of the fibre. Inside a single fibre, the myofibrils were sometimes so strongly basophilically stained and coarsely delineated as to resemble calcification.

Changes in Muscle Cell Nuclei.—All preparations from the infected mice showed an increased number of muscle cell nuclei. Normal spindle-shaped homogeneous nuclei located inside the sarcolemma were observed, and more frequently circular or oval nuclei with a clearly visible nuclear membrane, and nucleoli with strongly basophilic chromatin particles. These circular nuclei were usually to be found centrally in slender basophilic muscle fibres (Fig. 6). The nuclei lay in long chains of up to thirty in each fibril (Fig. 7). At one end of the row, the nuclei were tightly congested during amitotic division, and increasing distances between the nuclei represented the transition to normal muscle cell nuclei. In single cases mitotic division or states of pyknotic and karyorrhectic degeneration were noticed.

Changes in Sarcolemma.—The most pronounced changes took the form of an increase in the number of sarcolemma nuclei, and varying thickness of sarcolemma. Frequently the sarcolemma was intact and empty sarcolemma sheaths might be observed without tendency to collapse. In some cases, the sarcolemma was abnormally thick, and in others it was atrophic, permitting the entry of the interstitial round cells.

Ingress by Interstitial Round Cells.—This was observed in all preparations. The invasions were

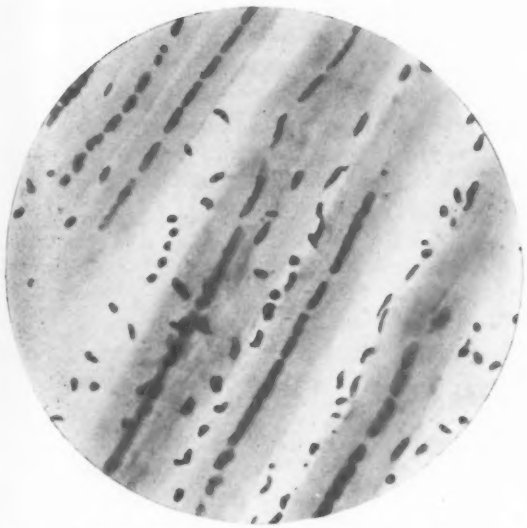

Fig. 7.—Longitudinal section of gastrocnemius muscle from C.-virus inoculated mouse. × 400. Note regeneration of muscle fibres, with slight affinity to stain, and nuclei arranged in longitudinal chains after amitotic division in centre of fibre.

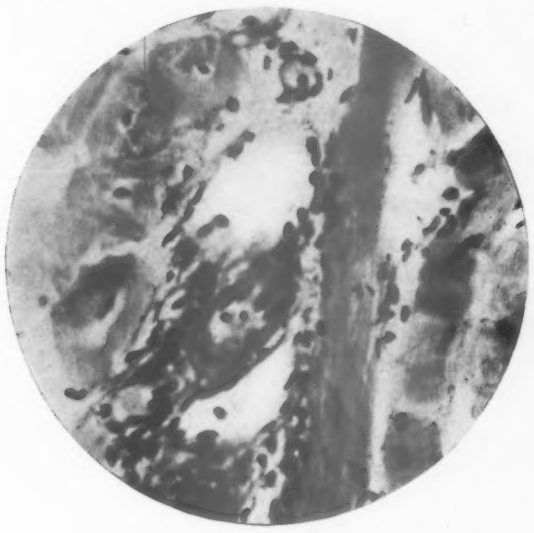

Fig. 8.—Perivascular infiltration of round cells.

perivascular, interstitial, and interfibrillar (Fig. 8). In young mice, the perivascular invasion seemed to be more frequent and more massive than the interstitial form.

Oedema.—This was pronounced in nearly all the preparations.

Hyperplasia of Lymph Nodes.—In a number of preparations hyperplasia of solitary interstitial nodes was seen.

Summary of Histopathological Findings

The histopathological changes observed may be divided into three aetiologically different groups:

(*a*) degenerative,
(*b*) inflammatory,
(*c*) regenerative.

(*a*) *Degenerative Changes.*—These manifest themselves in the muscle fibres with a tendency to abandon their longitudinal growth: the fibre twisting and folding within the sarcolemma sheath.

The fibre thus coiled or twisted then becomes "laced off" tending to degenerate piecemeal. Changes in the structure of the sarcoplasm are observed in the form of vacuolation and dissolution, during which the sarcoplasm presents a reticular structure. Furthermore, the entire fibre may be homogeneously transformed through a process of hyalinosis that in extreme cases may continue into calcification. During the process the striated structure disappears, either in certain parts or along the whole fibre. Generally, more or less pronounced longitudinal striation appears, the myofibrils becoming coarser and the basophilic staining stronger with tendency to fusion; in pronounced instances the myofibrils appear as longitudinal calcified streaks along the muscle fibre. Simultaneously changes occur in the nuclei which may become pyknotic and undergo karyorrhexis and karyolysis. These changes frequently take place within the intact sarcolemma, but sometimes the sarcolemma is damaged leaving a space through which an invasion of round cells may occur.

(*b*) *Inflammatory Changes.*—These may occur as interstitial oedema as well as round cell invasion, which entails increased numbers of histiocytes, lymphocytes, polymorphonuclear leucocytes, and mononuclear phagocytes. The invasion may be perivascular, interstitial, or interfibrillar. Hyperplasia of the regional lymph nodes may also occur.

(*c*) *Regenerative Changes.*—These comprise formation of hypertrophic fibres, increased appearance of longitudinal division of remaining healthy muscle fibres, or stretching and growth of the non-affected parts of a muscle fibre. Amitotic divisions of muscle cell nuclei arrange themselves in long chains around which develop basophil sarcoplasm, out of which myofibrils and, later, cross striations, differentiate. These fibres are more slender than those normally found, and they all have centrally arranged chains of nuclei.

The basophilism of the muscle fibres decreases with the formation of the myofibrils and the striated structure; the nuclei take up more peripheral

positions and become oblong and spindle-shaped and more homogeneous in structure. The amitotic division may frequently begin in a muscle cell nucleus surrounded by partly degenerated sarcoplasm. This nucleus and the new chain of nuclei may sometimes be connected through thin cytoplasmic cords.

These regenerative processes are rarely to be observed in their pure form. The average picture shows a confusion of degenerative, inflammatory, and regenerative processes, all stages of these three phases being seen within the individual muscle fibre.

Discussion

The histopathological changes found in these examinations confirm the observations of Melnick and others. They reveal no point of similarity to the changes appearing after infection by the virus of acute anterior poliomyelitis or in the muscles of a patient suffering from muscular dystrophies of spinal or neurological origin (Wohlfahrt and Wohlfart, 1935, 1936).

The lesions correspond on the other hand with what might be found in polymyositis (Christensen and Levison, 1950): inflammatory infiltration into the interstitial connective tissue and muscle fibres by polymorphonuclear leucocytes, lymphocytes, plasma cells, and histiocytes. The infiltrations were perivascular as well as diffuse. The muscle fibres showed irregular atrophy as in dystrophy of peripheral muscular origin. These changes also correspond to those found by Levison (1951) in biopsies from patients suffering from progressive muscular dystrophy.

The arrangement of the atrophic and hypertrophic fibres makes it believable that C.-virus infection—so far as it concerns muscle tissues—gives rise to a genuine muscular dystrophy. This leads to the question whether the changes ascertained in the last-mentioned group may be considered as more or less chronic manifestations of a previous virus infection.

Summary

Microscopic examinations of the gastrocnemius muscles of 22 albino mice inoculated with Coxsackie virus (Texas strain) were carried out. Nineteen healthy animals served as controls. The reaction to Coxsackie virus infection took the form of pronounced myositis.

Examinations by polarization microscopy revealed reduction and final complete disappearance of cross striation in the muscle fibres. These changes may affect the entire fibre, or certain areas only.

Pronounced degenerative, inflammatory, and regenerative changes were observed.

The dominant features of degeneration were sarcolysis, degeneration of the contractile parts of the sarcoplasm, degeneration of nuclei accompanied by pyknosis, karyolysis and karyorrhexis, dissolution and hyalinosis of the sarcoplasm, calcification, and phagocytosis.

Inflammation took the form of perivascular, interstitial, and interfibrillary changes, with invasion of inflammatory cells.

Regenerative changes appeared partly as amitotic division of muscle cell nuclei resembling sarcoplasts, and partly as increased longitudinal division of the sarcoplasm, besides proliferation and hypertrophy of non-affected sarcoplasm.

The histopathological changes observed make it likely that mice infected with Coxsackie virus react by developing genuine muscular dystrophy.

These studies were carried out with the co-operation of the Psychiatric Laboratory, University of Copenhagen (Dr. E. Christensen); the Neurophysiological Institute, University of Copenhagen (Dr. F. Buchthal); the State Serum Institute, Virus Department, Copenhagen (Dr. Herdis von Magnus); and the Military Hospital, Department of Physical Medicine and Rheumatic Diseases, Copenhagen (Dr. K. Jespersen).

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Altérations histologiques dans le sarcolemme et le sarcoplasma au cours de l'infection par le virus de Coxsackie

RÉSUMÉ

On examina microscopiquement le muscle gastrocnémien des 22 souris blanches infectées de virus de Coxsackie (souche de Texas). Dix-neuf animaux sains servirent de témoins. La réaction à l'infection par le virus de Coxsackie prit la forme d'une myosite prononcée.

L'examne au microscope polarisant révéla la réduction et finalement la disparition des stries croisées des fibres musculaires. Ces altérations portèrent sur la fibre entière ou bien sur des portions de celle-ci seulement.

On observa des réactions de dégénérescence, inflammatoires et régénératrices.

Parmi les traits principaux de la dégénérescence on cite: sarcolyse, dégénérescence des parties contractiles du sarcoplasma, dégénérescence des noyaux accompagnée de pycnose, caryolyse et caryorrhexie, fonte et dégénérescence hyaline du sarcoplasma, calcification et phagocytose.

L'inflammation se traduisit par des altérations périvasculaires, interstitielles et interfibrillaires avec invasion des cellules inflammatoires.

La régénération se manifesta sous forme de la division amitotique des noyaux des cellules musculaires ressemblant à des sarcoplastes, et aussi de la scission longitudinale augmentée du sarcoplasma, à coté de la prolifération et de l'hypertrophie du sarcoplasma sain.

Les altérations histopathologiques observées viennent à l'appui de l'hypothèse montrant que les souris infectées de virus de Coxsackie réagissent par une véritable dystrophie musculaire.

Alteraciones histológicas en el sarcolema y el sarcoplasma en el curso de la infección por el virus de Coxsackie

SUMARIO

Se examinó microscopicamente el músculo gastrocnemio de 22 ratones blancos inoculados con el virus de Coxsackie (cepa de Texas), con 19 animales sanos como testigos. La reacción a la infección por el virus de Coxsackie tomó la forma de una miositis pronunciada.

El examen al microscopio polarizante mostró la reducción y finalmente la desaparición de la estriadura cruzada de las fibras musculares. Estas alteraciones afectaron sea las fibras enteras sea ciertas de sus porciones.

Observáronse reacciones de degeneración, inflamatorias y regeneradoras.

Los rasgos dominantes de la degeneración fueron: sarcolisis, degeneración de las partes contractiles del sarcoplasma, degeneración de los núcleos con picnosis, cariolisis y cariorexia, disolución e hialinosis del sarcoplasma, calcificación y fagocitosis.

La inflamación tradújose por alteraciones perivasculares, intersticiales e interfibrilares con invasión de células inflamatorias.

La regeneración tomó la forma de división amitótica de los núcleos de las células musculares que se parecían a sarcoplastos y, en parte, de división longitudinal aumentada del sarcoplasma, al lado de la proliferación e hipertrofía del sarcoplasma sano.

Las alteraciones histológicas observadas ofrecen la probabilidad de que los ratones infectados con el virus de Coxsackie reaccionan con una verdadera distrofia muscular.

HEEL LESIONS OF RHEUMATOID ARTHRITIS

BY

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(RECEIVED FOR PUBLICATION DECEMBER 16, 1953)

Two lesions affecting the heel in rheumatoid arthritis have received little or no attention of recent years: one involves the plantar surface of the calcaneus and the calcaneal spur, and the other the synovial bursa between the insertion of the Achilles tendon into the calcaneus and the calcaneus itself. This note is designed primarily to draw attention to the sub-Achilles lesion, since it may be the presenting sign of rheumatoid arthritis and is often a major complaint: secondarily, to point out that the plantar surface of the calcaneus is often actively involved in rheumatoid arthritis and to indicate the nature of the involvement.

Normal Anatomy.—Normally (Fig. 1*a*, opposite), the Achilles tendon is inserted about 2 cm. below the upper surface of the calcaneus; the latter is covered with fibro-cartilage opposite the free tendon (Fig. 1*b*), and the bursal space is lined over the tendon by a thin synovium, and at its margins by synovium-covered fatty pads (Fig. 1*c*); there is a very small amount of viscous fluid. With advancing age, some cartilage degeneration occurs (Fig. 2); this is well described by Rossler (1896) on the basis of 225 bursae examined from about 140 cadavers of various ages. The bone, however, remains intact throughout life, and *x* rays show a smooth strong cortical layer.

Fig. 2.—Bone, showing cartilage degeneration in later life.

The plantar surface of the os calcaneus (Fig. 3) is

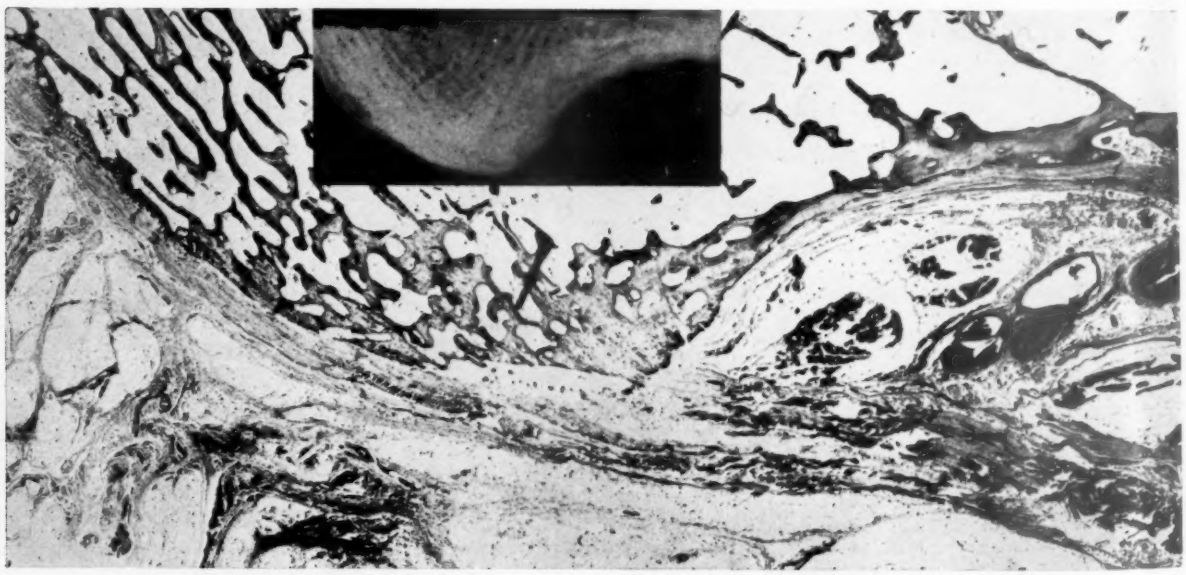


Fig. 3.—Plantar surface of calcaneus (× 7) in normal female aged 36, with *x* ray inset. Note smooth cortical bone.

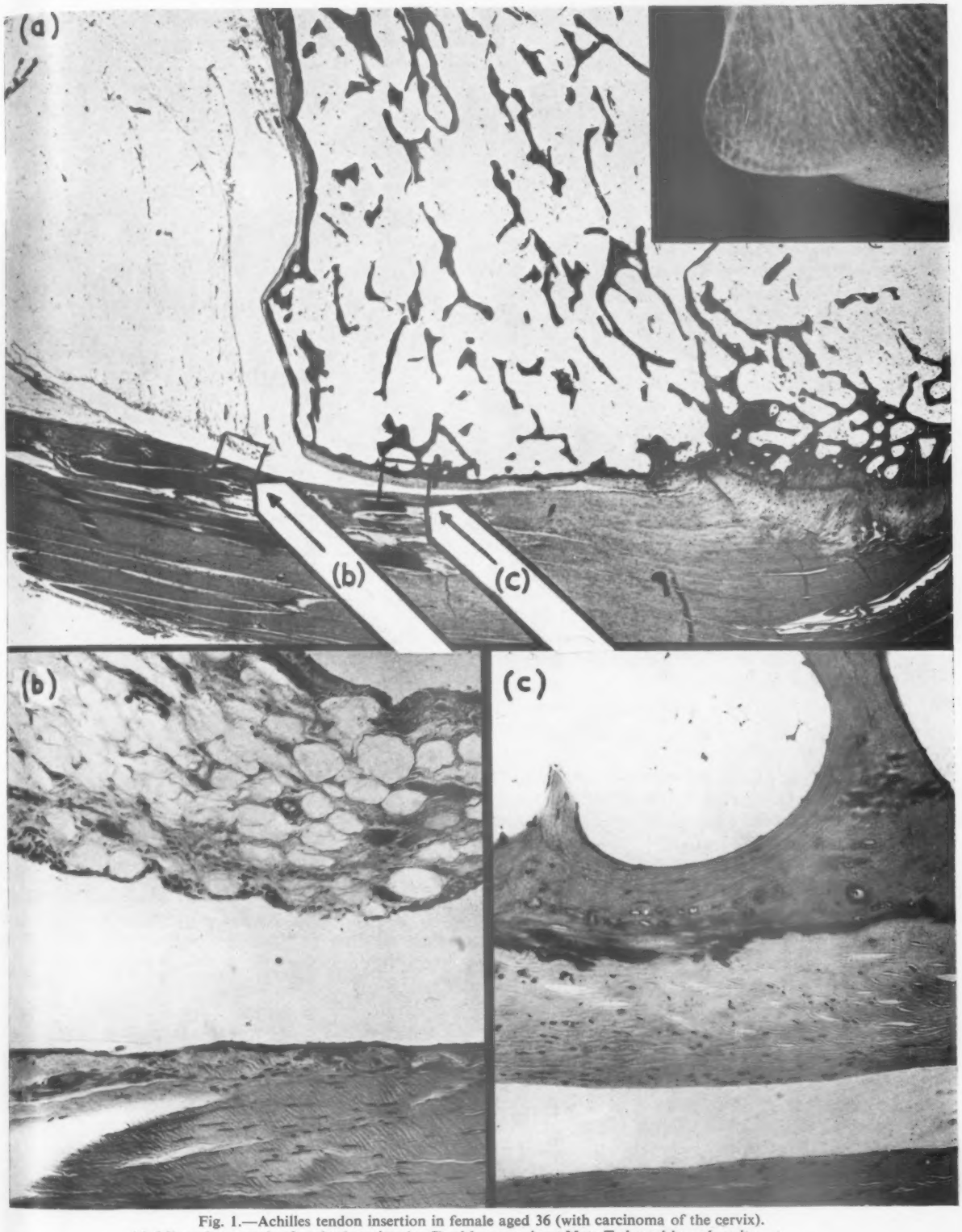


Fig. 1.—Achilles tendon insertion in female aged 36 (with carcinoma of the cervix).
(*a*) Microphotograph of sagittal section (× 7) with *x* rays inset.Note T-shaped bursal cavity.
(*b*) High-power view of marked area showing intra-bursal fat pad and synovial cells covering it (× 130).
(*c*) High-power view of marked area of fibro-cartilage covering bone (× 130).

covered by dense periosteum into which are inserted posteriorly the Achilles tendon and anteriorly the plantar aponeurosis. In between, the heel rests on a cushioned pad of fat interlaced with strong fascial sheets. Plantar spurs are seen in many people, the incidence increasing with age, without any complaint relating thereto; they consist of an extension of bone into the periosteal insertion of the plantar aponeurosis.

Incidence.—In the past 7 years 22 patients have complained of pain or swelling, or both, in the heel; in all except one radiological changes were visible. All, except one with synovial chondromatosis of the sub-Achilles bursa, were suffering from rheumatoid arthritis, as judged either by the actual presence at that time of other clinical and radiological criteria or by their development in the next few years. The incidence is probably of the order of 2-3 per cent., since, in an unselected series of 250 patients with rheumatoid arthritis, seen between 1939 and 1948 and followed to the present time (Dresner and Bywaters, 1953), six complained of painful heels and showed these lesions radiologically.* These six are included in the 21 mentioned above. Two others of the 21 in the series showed plantar-spur formation and ossification of the Achilles tendon only, without erosions, and these were not considered further. The Table (opposite) gives details of the group of nineteen cases with rheumatoid arthritis, radiological erosions being seen in eighteen of them. It will be noted that nine are female and ten male, a reversal of the usual sex-ratio. The patients' ages at the time of the heel lesion ranged between 21 and 65 years (usually in the 30s and 40s). The erythrocyte sedimentation rate was raised at the time in eleven of the nineteen and normal in eight.

Clinical Features

Sometimes the complaint of heel tenderness came within a few months of the onset of rheumatoid arthritis (four patients), and might even be one of the presenting symptoms, as in Cases 1 and 2.

Case 2, male, aged 32, complained of pain in back, feet, and ankles in July, 1945. Examination one month from onset revealed pain and swelling in both ankles, the left knee, and the metatarsophalangeal joint of both big toes. There was tenderness over both Achilles tendons and soreness of the plantar surface of both heels. The erythrocyte sedimentation rate was 105 mm./hr (Westergren).

One year later he was back at work, with no pain in the heels but some in the forefoot. Improvement continued and the erythrocyte sedimentation rate fell to 25 mm. in 1947, and to 18 mm. in 1950, but there was occasionally some pain in both heels and tenderness over the os calcis.

Fig. 4 shows the appearance of erosions beneath both Achilles tendons and beneath the heels; these had healed on the left by 1950, but left spurs not present originally.

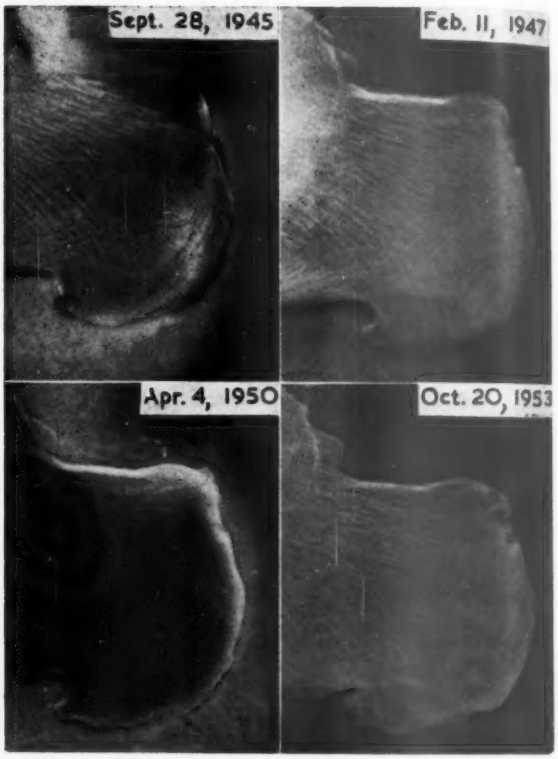


Fig. 4.—Case 2, heels: at onset, and during the following 8 years. Note bilateral sub-Achilles and plantar erosions.

The sub-Achilles bursal lesion produces pain on walking and on pressure of the shoe: tenderness is elicited by pressure on the posterior surface of the calcanean bone at the insertion of the tendon. This tendon itself appears to be broader and flatter than usual or may present a localized swelling near its insertion. Beneath it is felt a large fluctuant mass, occupying the space between tendon and ankle and protruding on either side of the tendon. Attempts to withdraw fluid by needling were unsuccessful in three cases. These lesions were bilateral in two cases; Fig. 5 (opposite) shows the appearances in Case 9. In a number of cases the lesions were accompanied by plantar calcaneal erosions (Table).

The plantar lesions manifest themselves with pain and tenderness, but without swelling.

Both types of lesion may remain tender on and off for years, but more usually the tenderness and the

* Those without complaint were not *x*-rayed.

TABLE

PARTICULARS OF NINETEEN PATIENTS WITH RHEUMATOID ARTHRITIS

Case No.	Hospital No.	Sex	Age (yrs)	Differential Sheep-cell Agglutination Titre	Erythrocyte Sedimentation Rate (Westergren)	Nodules (X or O)	Affected Tarsus or Metatarso-phalangeal		Time since Onset of Heel Lesions (yrs)	Location of Lesions			
										Sub-Achilles		Plantar	
							R	L		R	L	R	L
1	T. 07468	M	40	1 : 32	31	X	R	L	0	O	O	R	L
2	H. 57175	M	32	1 : 8	105	O	R	L	1/12	R	L	R	L
*3	T. 27636	F	65	1 : 32	37	O	O	L	3/12	R	O	O	O
4	T. 20123	M	39	1 : 8	6	O	R	L	4/12	O	L	O	L
5	H. 59756	F	56	1 : 256	36	X	O	L	6/12	R	O	O	O
6	T. 18367	M	21	—	15	O	R	L	1	O	L	O	O
7	T. 17264	M	45	1 : 8	21	X	R	L	2	O	L	R	L
8	T. 23117	M	24	1 : 1	15	O	O	O	2	O	O	R	L
9	H.101980	F	35	1 : 16	35	O	R	L	2½	R	O	O	O
10	H. 72396	M	21	—	10	O	R	L	3	R	O	O	O
11	T. 16352	F	43	1 : 4	27	O	R	L	3	O	L	O	O
12	H.131886	F	35	1 : 128	33	X	R	L	5	R	O	O	L
13	H. 54262	F	48	1 : 32	43	X	R	L	5	R	O	R	L
14	H. 33924	M	46	—	100	X	R	L	6	O	L	O	O
15	T. 10551	F	50	1 : 16	6	O	O	O	9	O	L	O	O
16	H. 74648	M	39	1 : 16	102	X	R	L	10	R	O	R	L
17	H.148476	F	40	1 : 2	18	X	R	L	11	R	O	O	O
18	T. 24020	M	25	1 : 4	9	O	R	O	12	O	L	O	O
19	H. 68196	F	33	1 : 32	12	X	R	L	13	R	L	O	O

* No bony *x*-ray change.

swelling disappear after a few years leaving radiological but no functional residua. In this they differ from the lesions of diarthrodial joints. It may be noted (Table) that, in the three cases where there is unilateral metatarsal or tarsal involvement, the associated sub-Achilles lesion is also unilateral but on the opposite side. This may be coincidence, but it may possibly represent a localization due to extra use; in a similar way we have often noticed that where olecranal nodules are unilateral, the opposite shoulder is usually affected but not the ipsilateral one.

The Table also shows that there is little correlation between the presence of plantar erosions and either nodule formation elsewhere or a raised sheep-cell agglutination titre.

Radiology.—The earliest radiological sign of a sub-Achilles lesion is in the soft tissues. The tendon becomes thicker on lateral view and the clear space beneath it, normally occupied by radio-translucent fat, becomes opaque owing to the presence of inflammatory cells, fluid, and blood vessels (Case 5, Fig. 6, overleaf).

At the same time, a rarefaction appears in the subjacent bone, and the sharply defined layer of subchondral cortical bone becomes less well defined and fuzzy. Finally, well-marked erosions, maximal just above the upper end of the insertion of the tendon, appear; this change may be quite rapid, as in Case 11 (Fig. 7, overleaf), where the interval between the first and second *x* rays was only 4 months, the first picture being taken within 4 weeks of the onset of pain and swelling. After a period of years, healing sets in, which is witnessed radiologically by remineralization of the bone and disappearance of the abnormal soft tissue thickening.

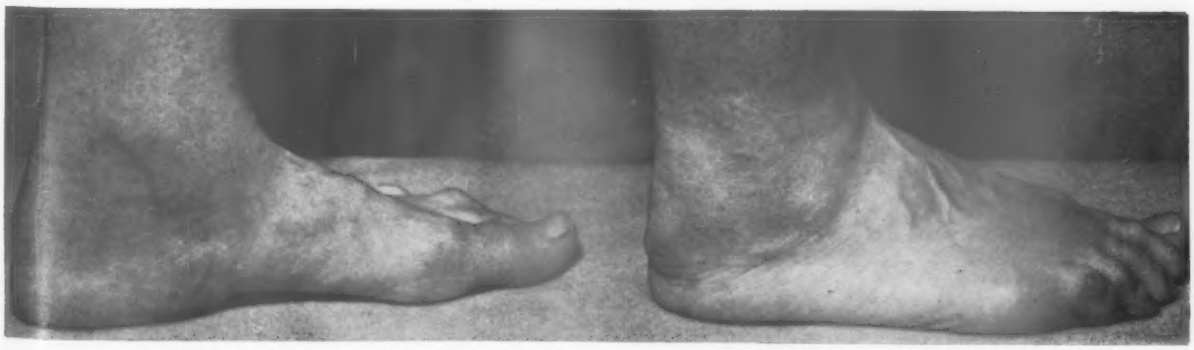


Fig. 5.—Case 9, bilateral swelling in, under, and to each side of Achilles tendon, present for 1 month.

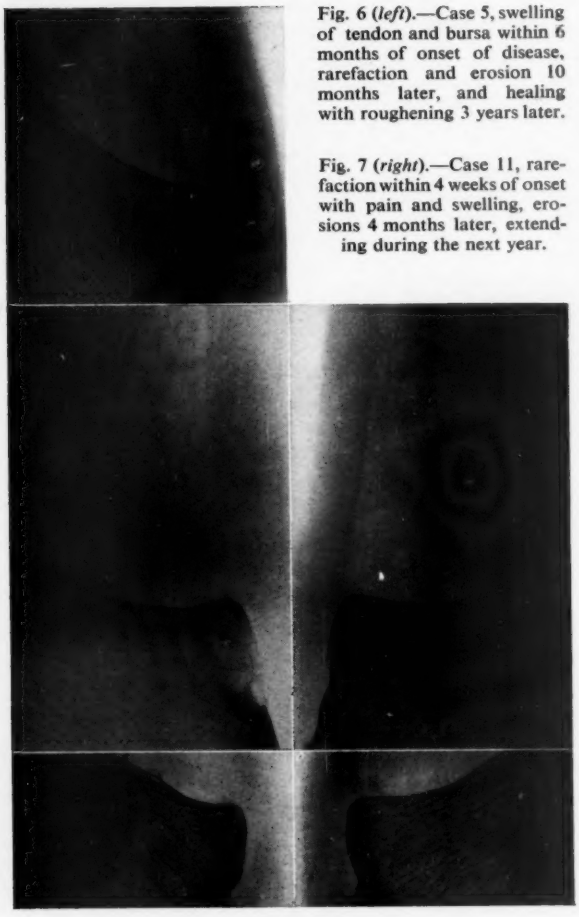
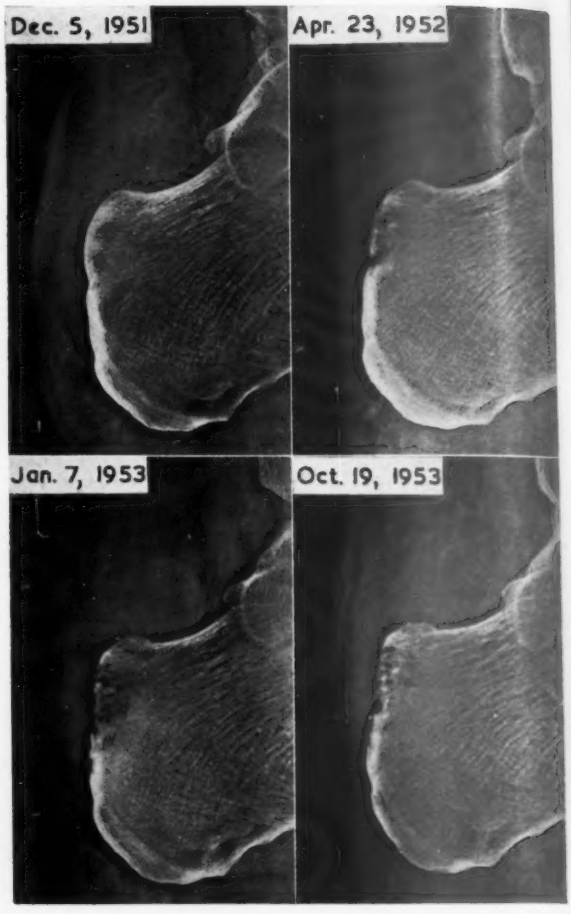


Fig. 6 (*left*).—Case 5, swelling of tendon and bursa within 6 months of onset of disease, rarefaction and erosion 10 months later, and healing with roughening 3 years later.

Fig. 7 (*right*).—Case 11, rarefaction within 4 weeks of onset with pain and swelling, erosions 4 months later, extending during the next year.



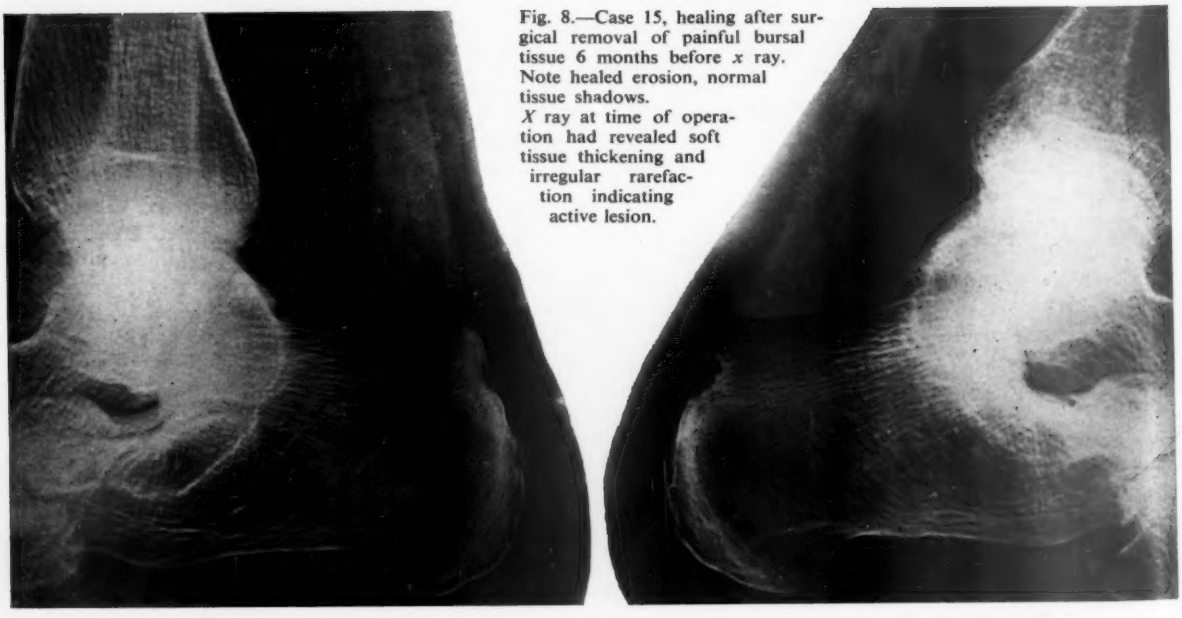


Fig. 8.—Case 15, healing after surgical removal of painful bursal tissue 6 months before *x* ray. Note healed erosion, normal tissue shadows.
X ray at time of operation had revealed soft tissue thickening and irregular rarefaction indicating active lesion.

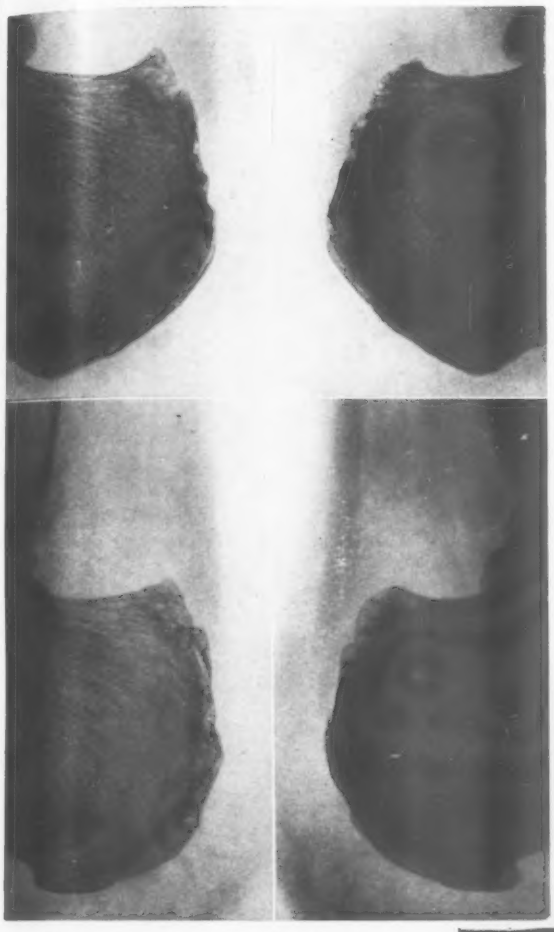


Fig. 9.—Case 19, erosions of whole subchondral surface and development of small spurs between May, 1951, and June, 1952.

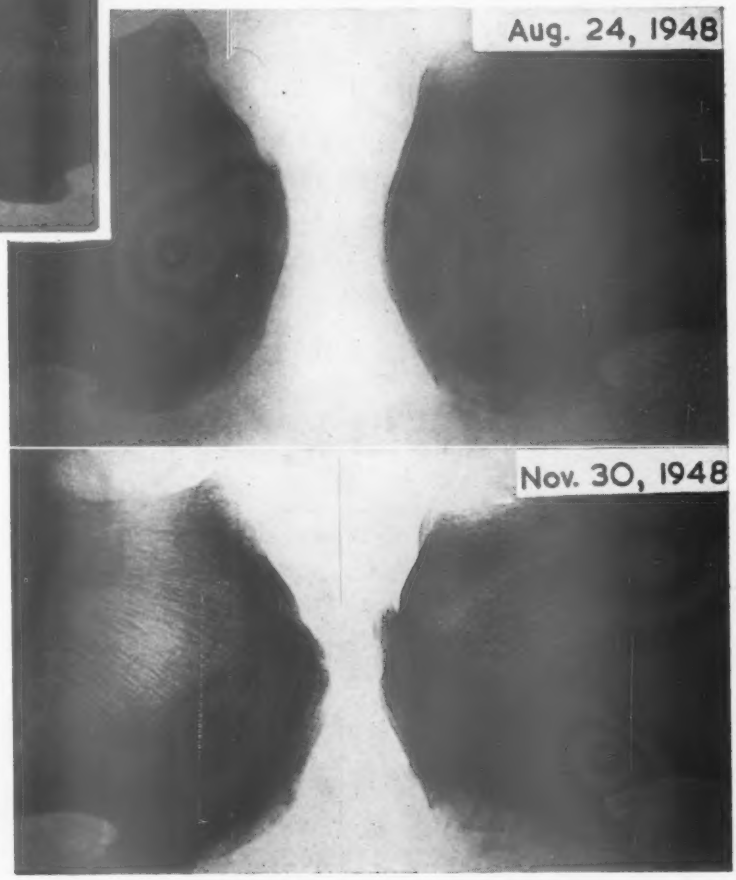


Fig. 10.—Case 13, progressive destruction of plantar surface of bone between August and November, 1948.

A permanent erosion scar is usually left as in Case 15 (Fig. 8), although in some patients no actual defect remains and the only sign of previous damage is a roughening of the cortical bony outline (Fig. 6). In others, defects occur all along the sub-tendinous surface from insertion up to the free edge (Case 19), (Fig. 9.)

The plantar lesions consist solely of an erosion of bone, often occurring over an area of 1-2 cm. from the joint behind the spur backwards; they appear first as rarefactions and finally as clear spaces, somewhat moth-eaten in appearance.

The plantar spur is usually involved and lengthened (Case 13, Fig. 10), or it may appear for the first time as a result of this process.

The last figure illustrates well the major destruction that may occur to a depth of apparently up to 1 cm. into the bone.

Pathology.—Biopsy has been performed on three patients and an autopsy examination on one. The biopsies showed a mass of rheumatoid granulation tissue, hyperplastic membrane, and large collections of plasma cells and lymphocytes embedded in a mass of myxomatous connective tissue.

In some areas the synovial membrane bore some resemblance to the later stages of a rheumatoid nodule, where the palisade layer comes to lie on

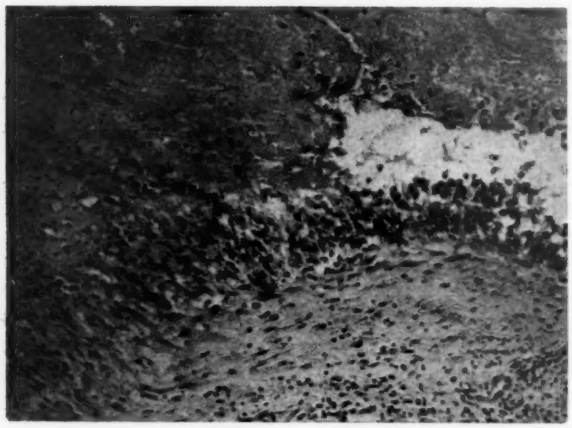


Fig. 11.—Case 15, Photomicrograph of bursal lining cells. Haematoxylin and eosin (× 100).

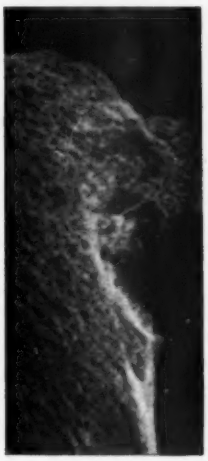
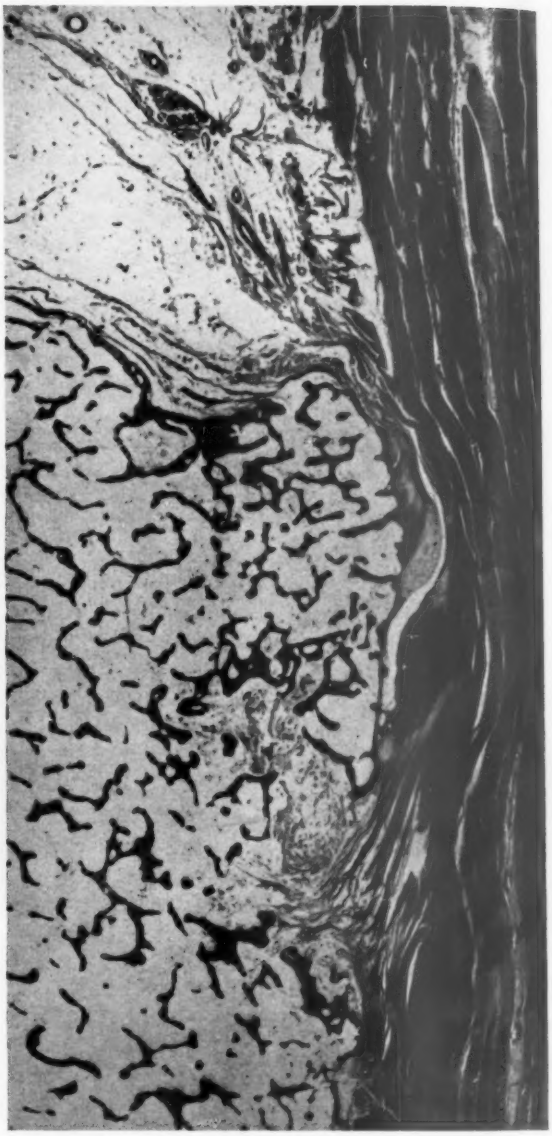


Fig. 12.—Case 16, Photomicrograph of sub-Achilles erosion and bursal obliteration in healed stage (reticulin × 7) with *x* ray of same area (× 2·5) inset.



the free surface of a cavity (Case 15, Fig. 11).

The autopsy specimen was from Case 16, a man dying with cor pulmonale, who had had rheumatoid arthritis for 13 years, and 3 years before death developed soft tissue swelling and erosion of the right sub-Achilles area and both plantar regions of the os calcis (Figs 12 and 13). Dissection showed complete obliteration of the sub-Achilles space. A sagittal section is compared with the *x* ray of a sagittal slice at death, and with the *in vivo* lateral *x* ray taken 3 years before. It shows that the acute inflammatory process has subsided, leaving residual blood vessels of the fatty pad,

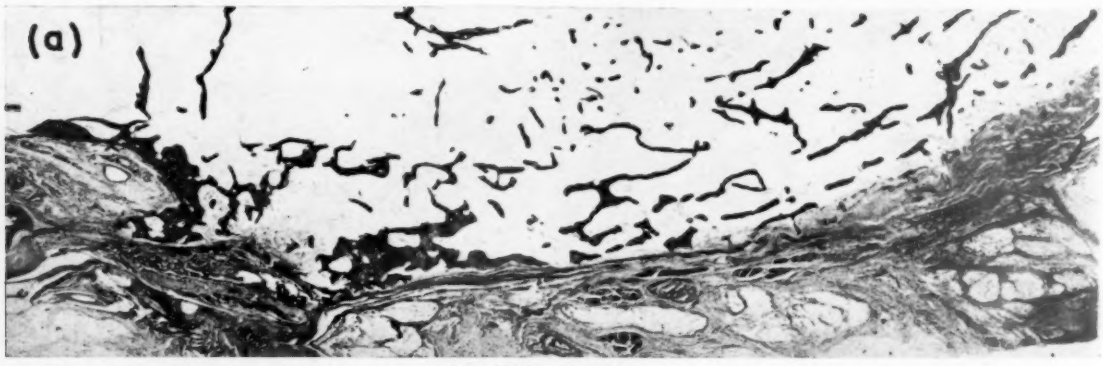


Fig. 13(*a*).—Case 16.
Photomicrograph of plantar surface of calcaneus, fibrinoid lattice work, and bone erosion. Haematoxylin and eosin × 5).

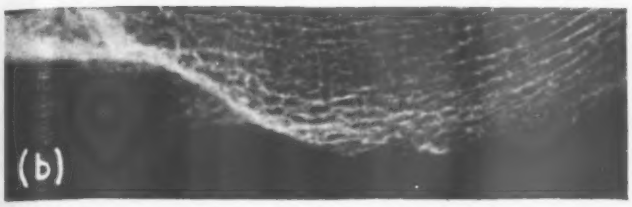


Fig. 13(*b*).—Case 16, *x* ray (× 2–5).

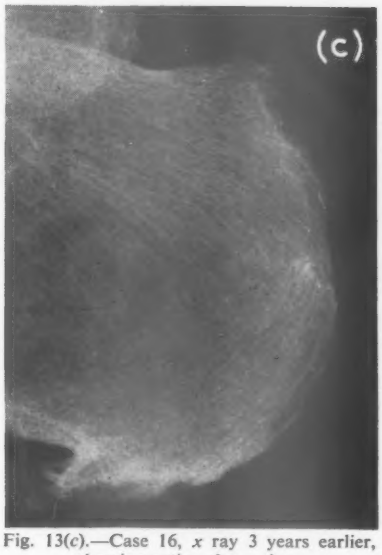


Fig. 13(*c*).—Case 16, *x* ray 3 years earlier, showing active absorption.

obliteration of the space, and a healed erosion of bone above the upper part of the tendon insertion, with loss of cartilage except at this site.

Dissection of the plantar surface of both right and left bones revealed a hyperaemic and rough (gritty) periosteal layer in this region overlaid by and densely adherent to an opaque yellow layer between it and the cushion of fat. Microscopically (Fig. 13*a*) this layer is seen to be fibrinoid and arranged in a lattice-work, invading bone from which it is separated by a vascular layer of cellular proliferation. It is sometimes arranged in a palisade (Fig. 14) and

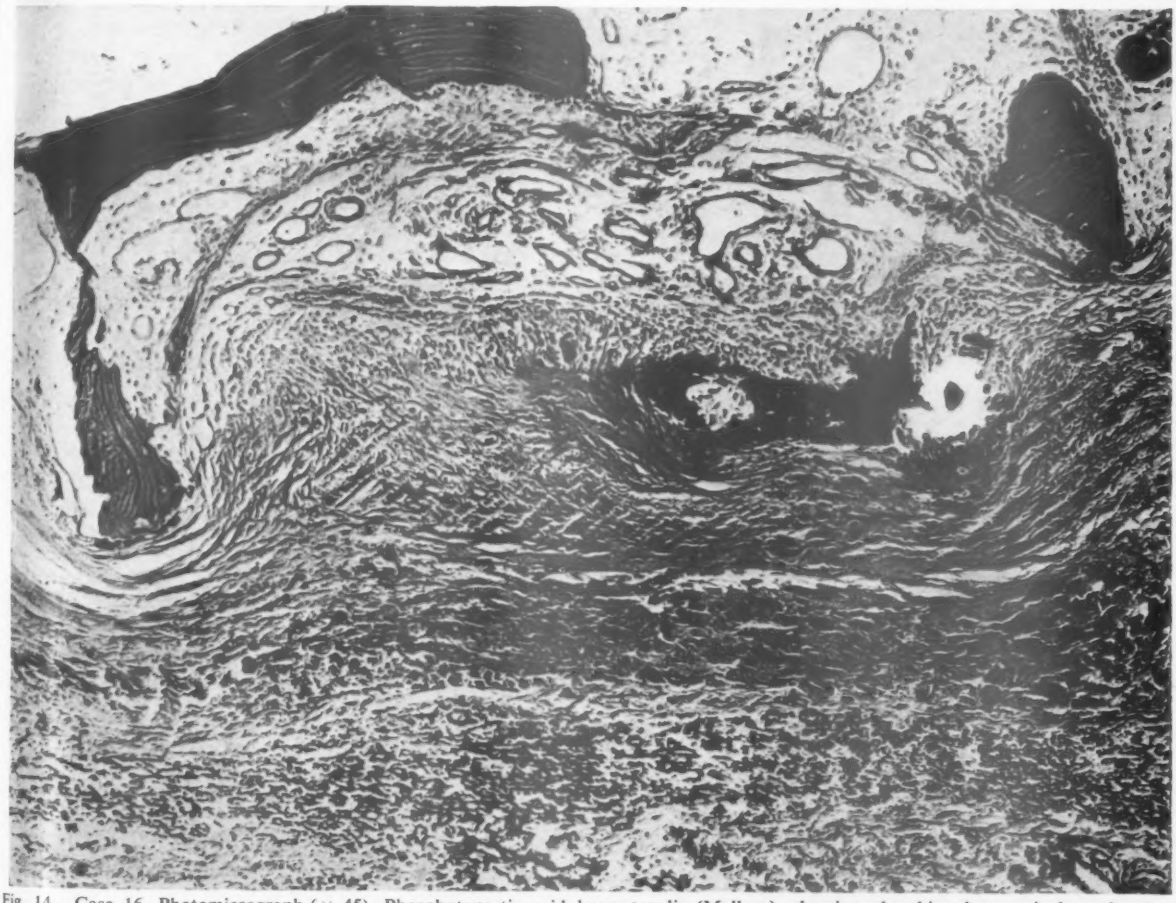
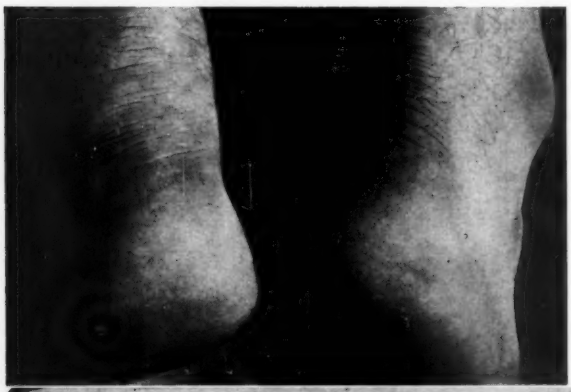


Fig. 14.—Case 16, Photomicrograph (× 45). Phosphotungstic acid haematoxylin (Mallory), showing absorbing bone spicule and osteoclasts, fibrinoid lattice work, necrobiotic nodule including necrotic bone and surrounding palisade layer, grossly hyperaemic area between this layer and the intact bone.

sometimes more loosely, but morphologically it obviously represents nodular tissue, to which it corresponds tinctorially, when stained with haematoxylin and eosin, toluidine blue, periodic acid Schiff, silver impregnation, and Mallory's phosphotungstic acid haematoxylin. Bone spicules were largely eroded away, some remaining partly surrounded by osteoclasts, and others buttressed by fresh layers of bone.

Differential Diagnosis of Sub-Achilles Swellings

The only patient in this series who did not have rheumatoid arthritis showed calcification radiologically in the sub-Achilles swelling (Case 20, Fig. 15), and, when this was excised, it proved histologically to be a synovial chondromatosis. Other tumours and infections (*e.g.* tuberculosis: Blencke, 1908; Wiesinger, 1896) may of course also occur, but we have not met them. Ossification in the Achilles tendon is an occasional cause of swelling and pain (Haglund, 1928). The lesion must also be differentiated from the peritendinous cellulitis described by Raynal (1883), which is probably traumatic in origin.



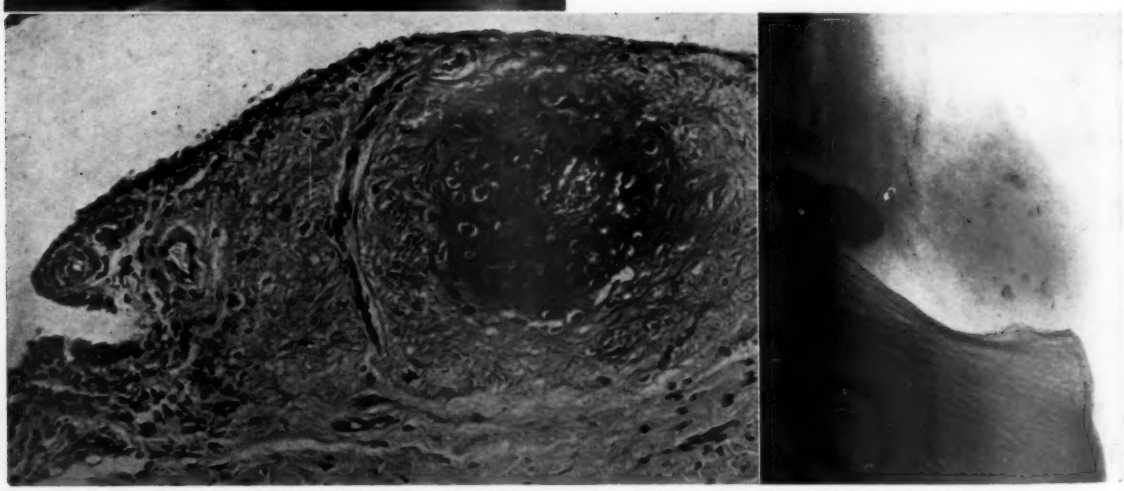


Fig. 15.—Case 20 (not in Table).
(*a*) Heels.
(*b*) Photomicrograph. Haematoxylin and eosin (× 105).
(*c*) *X* ray showing synovial chondromatosis of sub-Achilles bursa.

Treatment

Treatment in these patients is directed towards the generalized joint involvement. Specific local measures are sometimes necessary, particularly when these lesions are the only ones causing symptoms. In mild cases, the sub-Achilles swelling may be treated conservatively since it usually heals in a few years without residual damage, but if it causes severe pain or disability (as in Cases 5, 11, and 15) it is better excised, which procedure led in these three patients to considerable improvement in function. The plantar lesions are probably due in part to excessive use of the heels since they are frequently associated with metatarsal lesions. The provision of a soft pad beneath the heel or a padded ring usually gives the patient some relief.

Discussion

Sub-Achilles bursitis was first described by Albert (1893), who called it "achillodynia". Nine of his cases were later described by Rössler (1896), together with another in which the swelling was extirpated and examined. Only two of these cases gave a history of rheumatism. After the introduction of *x* rays, many papers appeared in the German literature on the subject of heel pain and calcaneal spurs, in some of which sub-Achilles bursitis receives mention (Blencke, 1908; Jacobsthal, 1908; König, 1910; Rolly and Appelt, 1914). In a few cases of each series "rheumatism" is mentioned (*e.g.* in four out of the eight described by Jacobsthal), but it is

not possible to determine whether their patients had rheumatoid arthritis, rheumatic fever, gout, or spondylitis as we know these entities to-day. Even in the most recent publications mentioning achillodynia (*e.g.* Haglund, 1928; Berenwenger, 1930; or Tepper and Haspekov, 1939), the details given are insufficient to determine the type of rheumatism. In all of these older series the chief aetiological factor was thought to be gonorrhoea, followed by trauma, and a large number of other causes, including rheumatism, tuberculosis (Blencke, 1908; Wiesinger, 1896), syphilis (Schirren, 1902), influenza (Franke, 1895), gouty diathesis, etc.

The present series of lesions is, with one exception (a synovial chondromatosis), associated with and due to rheumatoid arthritis: this is not thought to be coincidental, or entirely accounted for by selection of patients. It is thought that rheumatoid arthritis is the most common cause of sub-Achilles bursitis and of erosive plantar calcaneal lesions, and that the two are often associated the one with the other.

Summary

Nineteen cases of rheumatoid arthritis with heel lesions are described clinically and radiologically. Pathological observations were made in three cases. The two lesions which not infrequently occur together are:

(*i*) a sub-Achilles bursitis which erodes the os calcis and finally obliterates the bursa,

(*ii*) an erosion of the plantar surface of the os calcis by fibrinoid-containing tissue closely resembling a rheumatoid nodule.

I am grateful to Mr. Arden who kindly referred several of these patients and allowed me to use his notes, to Dr. Glynn and Dr. Harrison for use of pathological material, and to Mr. Fiske for the photographs.

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Lésions du talon dans l'arthrite rhumatismale

RÉSUMÉ

On décrit au point de vue clinique et radiologique 19 cas d'arthrite rhumatismale avec des lésions du talon. Dans trois cas on a pu faire une étude anatomo-pathologique. On a trouvé deux sortes de lésions survenant assez souvent ensemble:

(*i*) une bursite sous-achilléenne, érodant le calcanéum et finalement oblitérant la bourse,

(*ii*) une érosion de la surface plantaire du calcanéum par un tissu contenant une substance fibrinoïde et ressemblant beaucoup à un nodule rhumatismal.

Lesiones del talon en la artritis reumatoide

SUMARIO

Se describe clínica y radiológicamente 19 casos de artritis reumatoide con lesiones del talón. En tres casos se pudo hacer un estudio anatomo-patológico. Encontráronse dos tipos de lesiones, muchas veces al mismo tiempo:

(*i*) una bursitis sub-aquílea causando la erosión del calcáneo y finalmente obliterando la bursa,

(*ii*) una erosión de la superficie plantar del calcáneo por un tejido conteniendo una substancia fibrinoide y muy parecida a un nódulo reumático.

CARCINOMA OF THE LUNG SIMULATING EARLY RHEUMATOID ARTHRITIS

BY

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(RECEIVED FOR PUBLICATION DECEMBER 14, 1953)

It is well known that lung affections may be accompanied by so-called hypertrophic pulmonary osteo-arthropathy, which seems to be almost regularly associated with mild joint symptoms. Bamberger (1889) and Marie (1890) first studied this syndrome, but little attention has been paid to the misleading resemblance of these joint symptoms to those seen in the early stages of rheumatoid arthritis, though individual cases appear in the literature (Craig, 1937; Fried, 1943; Ellman, 1947; Pattison and others, 1951; and Frank, 1952).

It was our main object to investigate how frequently the clinician finds difficulty in the differential diagnosis of the joint symptoms accompanying carcinoma of the lung.

Material

The first series included 1,008 patients (725 female and 283 male) hospitalized in the clinic from 1934 to 1948 under the diagnosis of rheumatoid arthritis. The average age was 50 years for the females and 45·1 years for the males. A closer analysis was made of the patients with lung infiltration, pneumonia, and similar affections, and with a history of rheumatoid arthritis of not more than 5 years' duration at the time of onset of the pulmonary changes. This period was considered sufficiently long to exclude carcinoma of the lung.

The second series comprised 106 patients (27 females and 79 males) hospitalized for carcinoma of the lung from 1949 to 1951. The average age was 60·2 years for the females, and 63·6 years for the males. A more detailed study was made of the cases with definite joint symptoms accompanied by objective articular changes.

Results

First Series.—Seventeen patients (eight females and nine males) were found with lung infiltration and a history of joint symptoms for not more than 5 years at the time of recognition of the pulmonary changes. The examinations excluded primary carcinoma of the lung in all but three of them. A diagnosis of atypical pneumonia or its complication was made in five cases; in a further five cases the lung infiltration was demonstrated to be tubercular. In *one* of the male cases there were metastases in the lungs from a carcinoma of the prostate. Severe bronchiectasis and amyloidosis were present in *one* case.

One patient excluded from this series had suffered for about 10 years from rheumatoid arthritis, and then the onset of carcinoma of the lung was accompanied by an exacerbation of the joint symptoms.

The three cases of carcinoma of the lung with

TABLE

CASES TREATED FOR RHEUMATOID ARTHRITIS IN WHICH THE CLINICAL PICTURE WAS LATER FOUND TO BE DUE TO BRONCHIAL CARCINOMA

Series	Case No.	Sex	Age at onset of rheumatoid arthritis symptoms (yrs)	Duration of joint and other rheumatoid arthritis symptoms before recognition of carcinoma (mths)	Erythrocyte sedimentation rate on hospitalization (mm./hr)	Haemoglobin (per cent.)	Maximum body temperature (° C.)	Time from onset of rheumatoid arthritis symptoms to death (mths)
1	1	M	54 (symptoms at 35)	6	55	pale	39·7	7
	2	M	57	7	105	68	37·8	24
	3	M	57	3	108	65	37·7	7
2	4	M	51	7	61	78-68	38·3	7
	5	M	57	8	122	57	38·0	20

arthritic symptoms are included in the Table (Cases 1-3).

Second Series.—Five patients showed a clinical picture resembling rheumatoid arthritis; in three of these the onset of rheumatoid arthritis had occurred 5, 11, and 15 years respectively before the tumour was recognized, and no aetiological connection between the two diseases seems probable. On the other hand, there was a simultaneous onset of symptoms in two cases, which are shown in the Table (Cases 4 and 5).

The diagnosis of carcinoma of the lung was definitely established in the five cases listed in the Table, yet all the patients complained of very considerable pain in the affected joints, and had originally consulted a physician for this reason. In all cases there was active swelling of the joints, the articular regions were febrile, movements were markedly restricted, and muscular atrophy was present especially in the small muscles of the upper extremities, but additional features deviated from the typical rheumatoid arthritis syndrome. Cough symptoms had been present in all cases before the joint affection, but were too mild to be considered an inconvenience. Chest *x* rays eventually revealed the presence of a lung process, but in Case 4 the first *x*-ray examination gave a negative result and the erroneous diagnosis was therefore retained for some time. Acromegalic features developed in two cases; this was by no means a coincidence, for the same observation has been made by others. Fried (1943) described four cases, in three of which definite eosinophilic cell hyperplasia of the hypophysis was found at autopsy. In our own series the *post-mortem* hypophyseal finding in Case 4 was also of the acromegalic type. The sex incidence also differs from that of rheumatoid arthritis. Palmar erythema was a common finding in our patients, but this affection is not rare in rheumatoid arthritis, and Jonsson (1952) regards it as a symptom of that disease.

Case Report

Case 4, a labourer, 51 years of age, was admitted to hospital on January 10, 1952, with joint symptoms of one month's duration. He complained of poor appetite and an indefinite distress in the stomach. He believed he had lost about 4 lb. in weight. Achylia was present, he admitted to an insignificant "smoker's cough" of about 3 months' duration, and his feet, hands, and lower jaw had much increased in size. The large and small joints of the extremities had all become painful and swollen, and the temperature was raised to 37·5° and 39° C.

Examination.—The face appeared acromegalic, the lower jaw being protruded, the cheekbones prominent, and the soft tissues of the ears and nose thick. The hands were large and spade-like (Figure). The joints most severely affected were both ankles, left knee (marked accumulation of synovial fluid), both wrists, right elbow, and phalangeal joints especially middle and proximal joints of the second and fourth fingers. The articular regions were swollen and hot, and movement was painful and restricted. Apart from these symptoms simulating rheumatoid arthritis, there was redness of the tips of fingers and toes, increased growth of their soft parts, and slight biconcavity and tenderness of the nails.

Figure.—Case 4, showing clubbed fingertips, swollen finger joints, and acromegaly.

Auscultation and percussion of the lungs yielded no pathological findings. Lung function appeared normal: vital capacity, 3·75 l.; complementary air, 1·87 l.; reserve air, 0·94 l.; tidal air, 0·94 l.; maximum respiration, 108 l./min. (92 per cent. of normal).

There was no cardiac abnormality. The blood pressure was 140/88 mm. Hg.

Radiology.—*X* ray showed scars of a surgical operation for the removal of a knife-point from the lower portion of the right lung, slight hypertrophy of the heart, and bilateral defective development of the first rib. The hilar regions did not appear to be pathologically involved. The joints showed changes typical of incipient arthritis, with periosteal thickening and calcification of the ulna, radius, and metacarpal bones. The sella turcica appeared slightly above normal size.

Laboratory Findings

Erythrocyte sedimentation rate 61 mm./hr.
Gonococcal complement-fixation test negative; Wasserman reaction negative.
Antistreptolysin O titre 1 : 160.
Total serum protein 8 per cent. (albumin 3·2, globulin 4·8).
Formol-gel test positive in plasma in 5 min. 12 sec.; negative in serum.
Blood sugar 100 mg. per cent.
Haemoglobin 12·05 g.; erythrocytes 4·3 million per c.mm.; leucocytes 11,300 per c.mm.; eosinophils 1·5 per cent.; neutrophil staff cells 1·0 per cent.; neutrophil polymorphonuclears 51·5 per cent.; lymphocytes 36·0 per cent.; monocytes 9·5 per cent.
Platelets 307,000 per c.mm.
Rest nitrogen 20 mg. per cent.
Urine analysis normal.
Electrocardiogram normal.
Field of vision normal.

Ninety drops tinct. belladonna caused a transient, marked aggravation of the joint symptoms with elevation of body temperature in 24 hrs, similar to the reaction of rheumatoid arthritis patients to large amounts of atropine (Järvinen, 1952).

The joint symptoms progressed and the patient's condition deteriorated more rapidly than is usual in rheumatoid arthritis; after 6 weeks he became highly febrile, with increasingly active joint symptoms. When the danger of ankylosis became apparent, the parenteral administration of cortisone was started, and the symptoms were rapidly allayed at first, but a daily dose of not *less* than 100 mg. was unable to prevent recurrence of the inflammatory symptoms. As the clubbing of the fingers and toes continued to progress, another radiological examination of the lungs was carried out. The presence of a tumour in the left hilar region was suspected, but bronchoscopy failed to establish the suspicion, and biopsy also gave a negative result. The patient failed rapidly, the anaemia increased in spite of blood transfusions, and he died on June 18.

Post mortem.—A large carcinoma with infiltration of the intrathoracic lymph nodes was found in the upper lobe of the left lung. An intact bronchial mucosa explained the negative bronchoscopic finding. The appearance of the hypophysis pointed to acromegaly, cellular degeneration was evident throughout the gland, with poor differentiation of the acidophilic cells; haemorrhages, haemoglobinogenic pigment, and oedema were present in the stroma; the cells were atrophic; no signs of a tumour were observable in the hypophysis.

Discussion

It is apparent that pulmonary osteo-arthropathy developing on the base of a carcinoma of the lung may cause difficulty in recognizing the true condition. Our investigation showed that three of a total of 1,008 cases (1 per cent. of the patients over 50 years old) treated for rheumatoid arthritis had carcinoma of the lung. Similarly, two of 106 known cases of carcinoma of the lung had at first been treated for rheumatoid arthritis. Hansen (1952) found joint symptoms in twelve out of 100 patients with carcinoma of the lung, and Alvarez (1948) reported a greater prevalence of mild joint symptoms than of bronchial symptoms. A careful examination should be made of the lungs of every patient who seeks medical aid with the clinical picture of early rheumatoid arthritis.

The clinical picture in such cases resembles idiopathic rheumatoid arthritis to such a degree that the question may be raised of a possible aetiological correlation of the arthritic conditions. The simultaneous occurrence of arthritic symptoms and carcinoma of the lung is evidently not a coincidence. Cases have also been reported in which the joint symptoms disappeared after successful surgical removal of a tumour of the lung (Brea, 1948; Alvarez, 1948; Hansen, 1952; Pavlovsky, 1947; Rottjer and others, 1946; Ellman, 1947; Frank, 1952). This observation indicates that the joint affections cannot be ascribed to metastases, and no metastatic tumours have been found in the joints on *post-mortem* examinations.

It seems probable that the rapid development of the lung process plays some part in the occurrence of the joint symptoms. The clubbing of fingers and toes associated with slowly developing lung processes and certain diseases of the heart is not accompanied by joint symptoms, though it seems probable that the clubbing itself is a mild form of pulmonary osteo-arthropathy.

The aetiological mechanism of pulmonary osteo-arthropathy and of the associated articular symptoms still remains obscure. Many investigators suggest a close connexion with neurogenic reflexes. Thus it has been observed that hilar neurotomy (without resection of the lung) allays the joint symptoms in these patients for as much as 6 months (Brea, 1948; Hansen, 1952). A similar effect has been found to follow the ligation of the pulmonary artery (Wyburn-Mason, 1948). It is well to remember in this connexion, however, that temporary recovery from rheumatoid arthritis has often been observed after major surgical operations on any part of the body. The possible role of the autonomic nervous system in the development of the joint symptoms should also be considered, since severe symptoms sometimes appear in the joints of the corresponding upper extremity in connection with periarthritis humeroscapularis and with cardiac infarction, presumably arising by way of reflex.

An analysis of the joint symptoms of patients with pulmonary osteo-arthropathy should also take into consideration the effect of possible hormonal disorders. Disturbed hypophyseal function is frequently reflected in such symptoms as acromegalic features, but on the other hand joint symptoms are frequently present with acromegaly, and the simultaneous occurrence of acromegaly and rheumatoid arthritis was reported by Jeanneney (1936).

Summary

This report covers 1,008 patients diagnosed as suffering from rheumatoid arthritis and 106 patients with bronchial carcinoma. In the rheumatoid arthritis group, a follow-up examination indicated that a bronchial carcinoma was probably the aetiological factor in the joint symptoms in three cases (0·3 per cent.; 1 per cent. of the patients over 50 years of age). The bronchial carcinoma group included two patients who had previously been

treated for rheumatoid arthritis, although the symptoms were probably caused by the lung process.

These findings indicate the importance of examining the lungs of patients presenting the symptoms of rheumatoid arthritis. In male patients with arthritic symptoms combined with acromegalic features and/or clubbing of the fingers and toes, carcinoma of the lung should always be suspected.

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Carcinome du poumon simulant le début d'une arthrite rhumatismale

RÉSUMÉ

Ce rapport comporte 1008 malades diagnostiqués comme souffrant d'arthrite rhumatismale et 106 malades atteints de carcinome bronchique. Dans le groupe rhumatismal un examen ultérieur indiqua qu'un carcinome bronchique était probablement à l'origine des symptômes articulaires dans trois cas (0,3%-1% des malades âgés de plus de 50 ans). Dans le groupe des carcinomes bronchiques se trouvaient deux malades qui avaient été traités pour une arthrite rhumatismale bien que leur symptômes auraient pu relever de processus pulmonaire.

Ces donnés indiquent l'importance de l'examen des poumons des malades présentant des symptômes d'arthrite rhumatismale. Chez un homme, des symptômes d'arthrite associés aux traits acromégaliques et/ou à la deformation noueuse des doigts et des orteils, devraient toujours faire penser à un carcinome pulmonaire.

Carcinoma del pulmón simulando una artritis reumatoide temprana

SUMARIO

Este informe comporta 1008 enfermos con el diagnóstico de artritis reumatoide y 106 enfermos con carcinoma bronquial. En el grupo reumático un examen ulterior indicó que un carcinoma bronquial constituyó probablemente el factor etiológico de los síntomas articulares en tres casos (el 0,3%-1% de los enfermos de más de 50 años de edad). En el grupo de los carcinomas bronquiales hubo dos enfermos que habían sido tratados por una artritis reumatoide aunque sus síntomas debiéranse probablemente al proceso pulmonar.

Estos resultados indican la importancia de examinar los pulmones de los enfermos que presentan síntomas de artritis reumatoide. En un hombre con síntomas de artritis asociados con rasgos de acromegalia y/o con dedos nodosos hay que sospechar un carcinoma pulmonar.

PURIFIED ACTH GEL

CONTROL OF THERAPY IN RHEUMATOID PATIENTS

BY

H. F. WEST

Sheffield

(RECEIVED FOR PUBLICATION JANUARY 4, 1954)

Brooks and Norymberski (1952) discovered that a certain group of corticosteroids could be oxidized by sodium bismuthate to 17-ketosteroids and so estimated as such. They named this group "17-ketogenic steroids" (17-KGS). The importance of this discovery lay in the fact that hydrocortisone, cortisone, and their known corticosteroid metabolites in urine are in fact 17-KGS. Norymberski (1952) subsequently developed a method for the estimation of 17-KGS in urine. This provided a notable advance in the assay of adrenocortical steroids, in that it measured a large and precise fraction of the urinary corticosteroid output and in doing so avoided the usual destructive, and/or unreliable, procedures for hydrolizing the steroid conjugates. The method described by Norymberski, Stubbs, and West (1953) has now been further simplified (Gibson and Norymberski, 1954) and can be easily undertaken by any hospital biochemical laboratory.

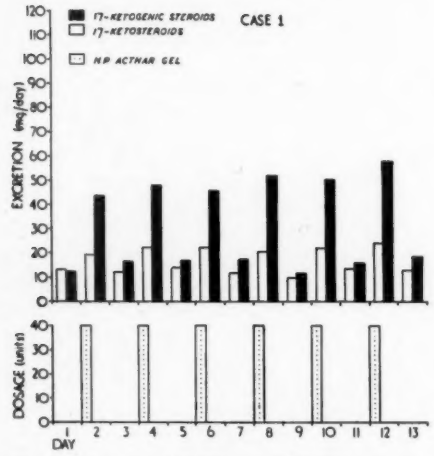

Fig. 1.—Output of 17-KS and 17-KGS in Case 1, a man aged 47, suffering from rheumatoid arthritis, on a dosage of 40 units H.P. Acthar Gel every 48 hrs intramuscularly, for 12 days.

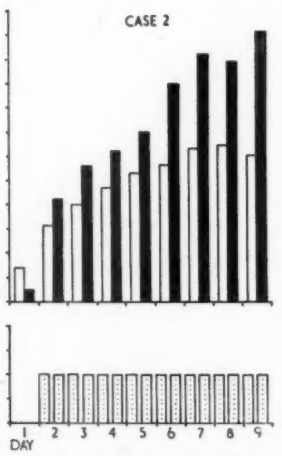

Fig. 2.—Output of 17-KS and 17-KGS in Case 2, a woman aged 42, suffering from rheumatoid arthritis, on a dosage of 20 units H.P. Acthar Gel every 12 hrs intramuscularly, for 9 days.

When hydrocortisone is given by slow intravenous transfusion, some 45 per cent. by weight is recoverable in the urine as 17-KGS. As hydrocortisone is the only known 17-KGS secreted by the adrenal, it is tentatively assumed that the increase in urinary 17-KGS that follows ACTH therapy reflects a parallel increase in hydrocortisone secreted by the adrenal. It is suggested that environmental changes may affect the percentage of hydrocortisone or cortisone metabolized to 17-KGS; so far this has not been observed in rheumatoid patients treated with cortisone, but it is a possibility that must be kept in mind. In the assay of 17-KGS we have a new research tool, which has already proved valuable in the control of ACTH therapy and in the differential diagnosis of endocrine disorders. One interesting application will lie in the differentiation between those environmental changes (? "stress") that call for an increased adrenal output of hydrocortisone and those that do not.

High purity ACTHAR gel (Armour) and purified corticotrophin gel (Wilson) were given to patients suffering from rheumatoid arthritis and ankylosing spondylitis. The degrees of adrenal stimulation induced were measured by the assay of urinary 17-KGS. The purpose of this paper is to report some of the results of these assays in twenty patients treated continuously with ACTH gel for periods of from 1 to 18 months.

(1) *H.P. ACTHAR Gel.*—40 "Units" given every 48 hrs by intramuscular injection (Fig. 1). The output of 17-KGS remains fairly constant after the first week, but the level varies considerably from patient to patient. It has

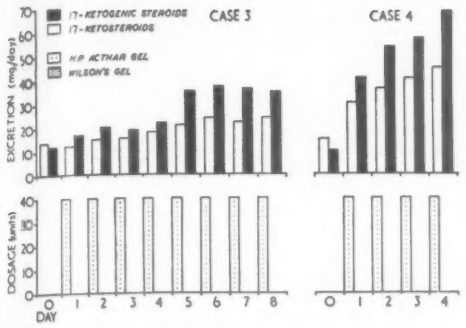

Fig. 3.—Output of 17-KS and 17-KGS in Case 3, a man aged 30, suffering from ankylosing spondylitis, and in Case 4, a man aged 36, suffering from rheumatoid arthritis, both on a dosage of 40 units Acthar Gel every 24 hrs intramuscularly, Case 3 for 8 days and Case 4 for 4 days.

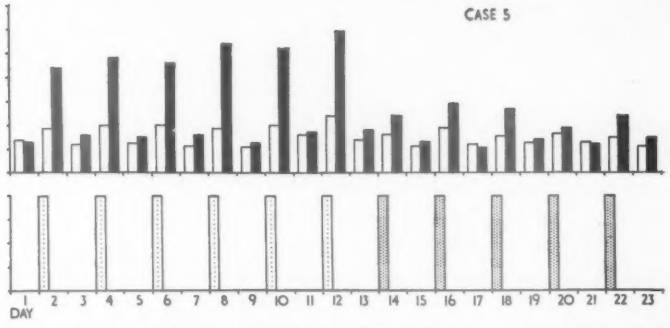

Fig. 4.—Output of 17-KS and 17-KGS in Case 5, a man aged 47, suffering from rheumatoid arthritis, on a dosage of 40 units H.P. Acthar Gel every 48 hrs intramuscularly for 12 days, followed by 40 units Wilson's Gel every 48 hrs intramuscularly for 10 days.

been observed as low as 20 mg. and as high as 50 mg. A low output is not due to the adrenal being unable to respond, since a marked increase will occur when the injections are given more frequently. The duration of the clinical benefit varies from 30 to 45 hrs, depending, it would seem, upon the severity of the disease and the degree of adrenal stimulation achieved.

(2) *H.P. ACTHAR Gel.*—20 "Units" given 12-hrly by intramuscular injection. By the end of the first week the output of 17-KGS was equal to what one would expect from an adrenal secretion of 250 mg. hydrocortisone daily. The progressive rise suggests that the preparation used contained an adrenal growth factor, since this rise cannot be accounted for by a simple additive effect. (Fig. 2.)

(3) *H.P. ACTHAR Gel.*—40 "Units" given every 24 hrs by intramuscular injection. The two patients were treated with the same batch of H.P. ACTHAR Gel. The assays show how greatly the adrenal stimulation achieved may vary from patient to patient in these circumstances. (Fig. 3.)

(4) *Comparison of Two "Highly Purified" ACTH Gels.*—This finding, which has been observed repeatedly, is shown because the "units" of both brands of ACTH Gel are considered to be equivalent. (Fig. 4.)

(5) *Pitfalls of Long-term Therapy.*—When ACTH is administered for a long time, its effectiveness in stimulating the adrenal cortex may diminish—though we have not seen this happen during therapy with H.P. ACTHAR Gel. On the other hand, with an increased dose, or with a change to a more potent preparation, the adrenal stimulation may increase and may do so progressively. In the case illustrated (Fig. 5), the patient was not able to return for examination

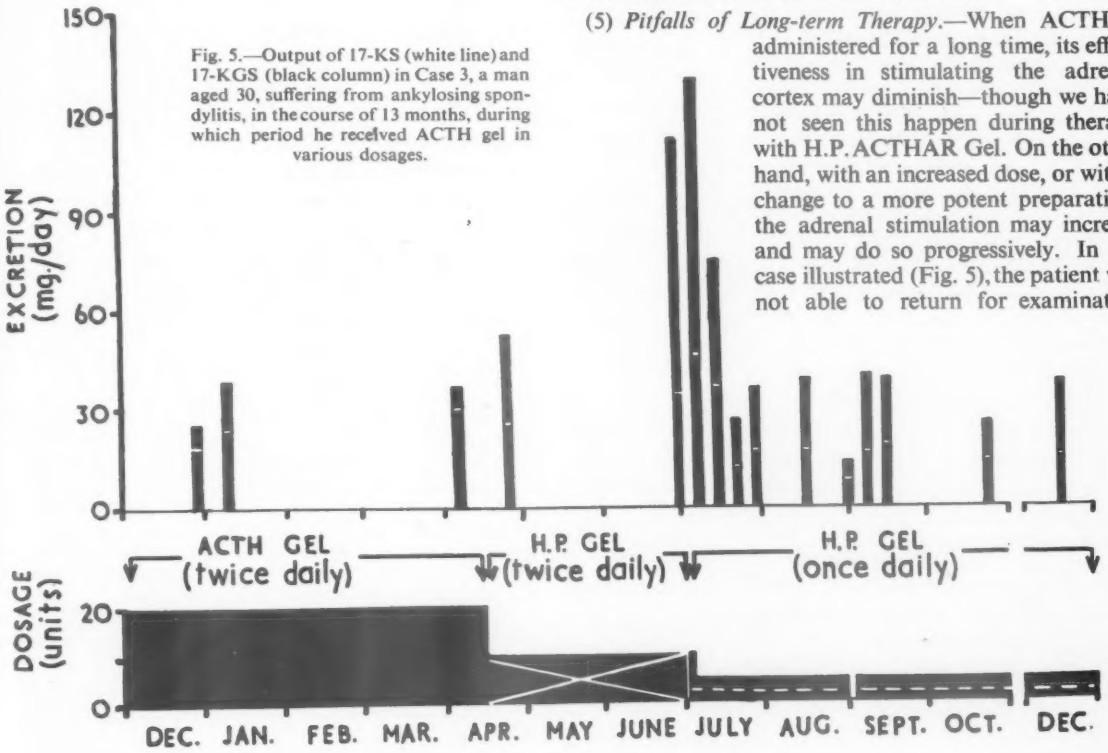

Fig. 5.—Output of 17-KS (white line) and 17-KGS (black column) in Case 3, a man aged 30, suffering from ankylosing spondylitis, in the course of 13 months, during which period he received ACTH gel in various dosages.

during the months of May and June. During this time the adrenal stimulation increased to dangerous levels. When he did return his diastolic blood pressure had risen from normal levels to 135 mm. Hg; 6 months later, at the time of the last assay, it had fallen to 115 mm. Hg.

The value of ACTH therapy to these patients has not been finally assessed, but it may be said that, at least during the initial weeks of treatment, the effectiveness is similar to what one would expect from cortisone given in corresponding amounts. For example, a daily injection of ACTH gel producing a urinary output of 40 mg. 17-KGS has the expected clinical effectiveness of 100 mg. cortisone acetate given by mouth.

Discussion

In the study of the use of ACTH it is not the amount given that matters but the level to which the secretion of corticosteroids is raised. In the first few days of treatment one can obtain a rough idea of the degree of adrenal stimulation by studying eosinophil counts and changes in electrolyte metabolism. After this time—unless steroid assays are made—one can only note the presence or absence of excessive stimulation. Various methods for assaying corticosteroids in blood and urine have been described, but to the best of our knowledge the only practicable and reliable assay of the adrenocortical function with which we are at present concerned in the treatment of rheumatic diseases, namely, the output of hydrocortisone by the adrenals, is that of the urinary 17-KGS.

Summary

17-ketogenic steroids (17-KGS) are corticosteroids that can be oxidized to 17-ketosteroids (17-KS) by sodium bismuthate. Hydrocortisone secreted by the adrenal cortex or administered hydrocortisone or cortisone are the only known sources for the 17-KGS found in urine. H.P. ACTHAR Gel and Wilson's Purified corticotrophin have been administered for prolonged periods to 20 patients suffering from rheumatoid arthritis and ankylosing spondylitis. The resulting increases in excretion of 17-KGS and 17-KS have been measured. Representative findings are recorded in graphic form. It is concluded that:

(1) The present method of describing the potency of an ACTH preparation for intramuscular injection is very unsatisfactory.

(2) The H.P. ACTHAR Gel used in these studies contained, in all probability, an adrenal growth factor.

(3) The use of a reliable method of assessing adrenocortical activity is essential for the intelligent use of ACTH.

I am indebted to Mr. George Gibson and to Mr. R. D. Stubbs for their skill in performing the steroid assays.

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Gel de ACTH purifié
Contrôle du traitement des rhumatisants

Résumé

Les stéroides 17-cetogènes (17-KGS) sont des corticostéroides qui peuvent être oxydés par le bismuthate de soude pour devenir 17-cetostéroides (17-KS). La hydrocortisone sécrétée par l'écorce surrénale et la hydrocortisone ou la cortisone administrée sont les seules sources connues des 17-KGS de l'urine. Le Gel H.P. ACTHAR et la corticotrophine purifiée de Wilson ont été administrés pour des périodes prolongées à 20 malades atteints d'arthrite rhumatismale et de spondylarthrite ankylosante. L'augmentation de l'excrétion des 17-KGS et des 17-KS qui en a résulté, a été mesurée. Les résultats représentatifs ont été enrégistrés sous forme de graphique. On conclut que:

(1) L'actuelle méthode de description de la force d'une préparation de ACTH pour injection intramusculaire est peu satisfaisante.

(2) Le Gel H.P. ACTHAR utilisé dans cette étude contenait, selon toute probabilité, un facteur surrénal de croissance.

(3) Une méthode précise d'évaluation de l'activité corticosurrénale est essentielle pour l'application intelligente de l'ACTH.

Gel de ACTH purificado
Control del tratamiento de los reumáticos

Sumario

Los esteroides 17-cetógenos (17-KGS) son corticoesteroides capaces de oxidación por el bismutato de sodio para formar 17-cetosteroides (17-KS). La hidrocortisona secretada por la corteza suprarrenal y la hidrocortisona o la cortisona administrada constituyen las únicas fuentes conocidas de los 17-KGS en la orina. El Gel H.P. ACTHAR y la corticotrofina purificada de Wilson fueron administrados durante períodos prolongados a 20 enfermos con artritis reumatoide y con espondilosis anquilosante. La resultante aumentación de la excreción de 17-KGS y de 17-KS fué medida. Los resultados representativos fueron anotados en forma diagramática. Se conclude que:

(1) El método presente de descripción de la potencia de un preparado de ACTH para inyección intramuscular no es muy satisfactorio.

(2) El Gel de H.P. ACTHAR empleado en este estudio contenía, en toda probabilidad, un factor suprarenal de crecimiento.

(3) Un método seguro de avaluación de la actividad corticosuprarrenal es esencial para el empleo inteligente de la ACTH.

A NOTE ON THE RAPID ASSAY OF 17-KETOGENIC STEROIDS IN URINE

BY

G. GIBSON and J. K. NORYMBERSKI*

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(RECEIVED FOR PUBLICATION JANUARY 14, 1954)

The determination of urinary corticosteroids by their conversion to 17-ketosteroids (17-KS) on treatment of urine with sodium bismuthate has been recently reported (Norymberski, 1952; Norymberski, Stubbs, and West, 1953). The group of corticosteroids thus determined has been termed 17-ketogenic steroids (17-KGS). The interest in this method shown by colleagues from other laboratories prompts us to communicate a modification of the original procedure by which a considerable saving of time is achieved. The alteration of the technique consists in reacting the surplus bismuthate with sodium metabisulphite instead of removing it by centrifugation. This simple expedient dispenses with several operations and enables the oxidation, hydrolysis, and extraction of urine to be performed in one reaction vessel. As in the original method, the estimations are carried out with duplicate runs, but from each run only one sample is taken for the Zimmermann reaction. It is now possible for one person to perform in one day the combined estimation of 17-KS and 17-KGS on six urine specimens.

* Holder of an Empire Rheumatism Council Research Fellowship during the period in which this work was done.

Experimental Procedure

Estimation of 17-KS.—This is performed as previously described (Norymberski and others, 1953). The addition of acetic acid to urine before hydrolysis is now found to be unnecessary.

Estimation of "Total 17-KS" (17-*KS*+17-*KGS*).—2 ml. urine, 2 ml. glacial acetic acid, and 0·5 g. sodium bismuthate are shaken for 30 minutes in a glass-stoppered centrifuge tube; care is taken to exclude direct daylight during this operation. 1 ml. 30 per cent. sodium metabisulphite solution, 4 ml. water, and 3 ml. concentrated hydrochloric acid are added and the tube is placed for 10 minutes in a bath of boiling water. After cooling in cold water, 10 ml. ethylene dichloride are added, and the tube is shaken for 15 minutes and centrifuged. The top layer is removed by suction and the extract is shaken first with 2·5 ml water for 2 minutes and then with 2·5 ml. 3N sodium hydroxide solution for 5 minutes. After each wash the layers are separated as described above. The washed extract is filtered through a fluted paper and a sample of 5 ml. is taken for the colorimetric estimation. All other experimental details are as previously described (Norymberski and others, 1953).

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EFFECT OF CERTAIN HYDROXYBENZOIC ACIDS ON THE OXYGEN CONSUMPTION OF WISTAR RATS

BY

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(RECEIVED FOR PUBLICATION JANUARY 28, 1954)

Despite the introduction of numerous other chemotherapeutic agents, salicylic acid and its derivatives retain an important place in the treatment of many rheumatic disorders; therefore any suggestion concerning their mode of action is of peculiar interest. Cochran (1952) has suggested that the increased tissue oxidation that he had observed after salicylate administration might be of fundamental importance in the therapeutic action of this drug. He gave 10 g. sodium salicylate intravenously to each of two normal subjects and to one patient with subacute rheumatism, and oral doses of 7·5 to 10 g. daily to three patients with subacute rheumatism; there was a marked increase in the oxygen consumption of about 60 to 70 per cent. after intravenous dosage and of 30 to 40 per cent. when the drug was given by mouth. This change in oxygen consumption was accompanied by a fall in the RQ, from which Cochran deduced that there was an increased utilization of protein or fat. Barbour and Devenis (1919) had previously studied the effect of oral doses of 1 to 1·25 g. acetylsalicylic acid on the metabolism of five normal men. They found that there was an average increase of 6·1 per cent. in oxygen consumption, whilst the carbon dioxide output increased concomitantly so that the RQ was unchanged. Denis and Means (1916) had reported a similar experiment with variable results.

Present Investigations

Since not only salicylic acid derivatives have been used in the therapy of rheumatic fever, but also other hydroxybenzoic acids such as the 2 : 6, and 2 : 5 dihydroxy compounds it was decided to study their effect on the oxygen consumption of the Wistar rat to establish whether there was any correlation between the stimulation observed and the known therapeutic efficacy in man.

Method.—The oxygen consumption of pairs of 150-200 g. male Wistar rats was measured by the closed circuit method of Maclagan and Sheahan (1950).

The drugs were given intraperitoneally in 1 ml. of either saline or 1 per cent. sodium carbonate at a dosage of 50 mg. per rat. A control group was injected with the vehicle only. The oxygen consumption of the treated group was measured over the succeeding 3-hr period and was expressed as a percentage of the mean oxygen consumption of the control group for that experiment.

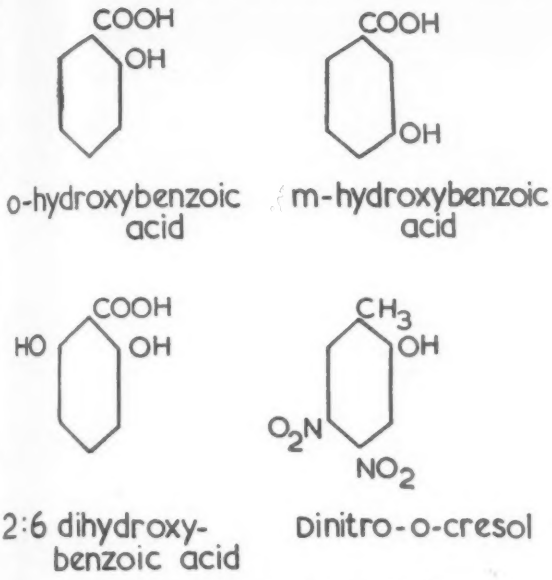
Results.—The Table shows that salicylic acid was unique in increasing significantly the oxygen consumption. The only other positive finding was that m.-hydroxybenzoic acid (see Figure, opposite) was notably depressant. The remaining compounds were without significant effect.

TABLE

EFFECT OF HYDROXYBENZOIC ACIDS ON OXYGEN CONSUMPTION OF RATS

Systematic Name	Trivial Name	No. of Observations	O_2 Consumption compared with Control Group 100 per cent. (with standard deviation)	Probability (Student's *t* test)
Benzoic		18	102 ± 10·2	—
*o-hydroxybenzoic	Salicylic	12	183 ± 16·4	< 0·001
*m.-hydroxybenzoic		24	65 ± 7·6	< 0·001
p.-hydroxybenzoic		24	92 ± 15·2	—
2 : 3 dihydroxybenzoic		18	101 ± 9·6	—
3 : 4 dihydroxybenzoic	Protocatecheuic	18	102 ± 20·8	—
2 : 5 dihydroxybenzoic	Gentisic	18	103 ± 19·4	—
*2 : 6 dihydroxybenzoic	γ resorcylic	18	106 ± 12·4	—
2 : 4 dihydroxybenzoic	α resorcylic	18	97 ± 13·8	—
cis-hexahydrosalicylic		18	103 ± 18·4	—

* See Figure for formulae.



Figure—Structural formulae of compounds discussed.

Discussion

Amongst the hydroxybenzoic acids, salicylic acid and its derivatives are most frequently used in the treatment of rheumatic fever.

Another compound, the sodium salt of 2 : 6 dihydroxybenzoic acid (Figure), has been reported by Reid, Watson, Cochran, and Sproull (1951) to be beneficial in doses lower than those of salicylate necessary to achieve comparable clinical results, but use of this compound was accompanied by many toxic manifestations.

Of questionable efficacy is 2 : 5 dihydroxybenzoic acid. This substance was reported as effective therapeutically both by Meyer and Ragan (1948), and by Camelin, Accoyer, Pellerat, Lafuma, and Coirault (1949), but subsequently Camelin, Accoyer, Vailhé, Roumagnac, and Rosset (1952) recorded an increase in the incidence of carditis in rheumatic disease during the use of this drug.

Amongst the remaining compounds tested, m.- and p.-hydroxybenzoic acids were described by Stockman (1920) as inactive in rheumatic fever.

Thus, of the two compounds, salicylate and 2 : 6 dihydroxybenzoic acid, reported to be useful in this disease, only the former had a stimulant effect on metabolism. Cochran's suggestion referred to above that the effect on metabolism is related to therapeutic value, therefore receives only partial support.

Baker (1936) pointed out that the dissociation constants of benzoic acid and of those mono-, di-, and trihydroxybenzoic acids, which do not possess an hydroxyl group in the ortho position, are less than 1×10^{-4}. Those acids having such an ortho hydroxyl group have dissociation constants considerably higher than this; the highest is that of 2 : 6 dihydroxybenzoic acid which has a value of $5{\cdot}0 \times 10^{-2}$. The increased acidity of the salicylic acid derivatives he ascribed to chelation of the anion. Reid and others (1951), in introducing 2 : 6 dihydroxybenzoic acid to clinical practice, suggested that this ability to chelate might be of significance in the therapy of rheumatic fever, an idea which was supported by the clinical efficacy of their compound. Thus there are two suggestions from the same department:

(*a*) that the therapeutic effect of salicylate is due to some, as yet undefined, stimulation of metabolism,
(*b*) that it is related to the ability of these compounds to form chelate rings.

It is apparent from the results given above that, in the rat at least, the increase in metabolism is unrelated to the dissociation constant of the hydroxybenzoic acids and hence to chelation, so that unification of these two concepts lacks experimental support.

The unique stimulatory action of salicylates amongst the hydroxybenzoic acids recalls the effect of the nitrophenols and related compounds. This similarity extends to observations on carbohydrate metabolism. Acute depletion of liver glycogen has been demonstrated to occur after the injection of salicylate into rats by Lutwak-Mann (1942), and by Smith, Meade, and Bornstein (1952). Bidstrup and Payne (1951) have reported that dinitro-ortho-cresol (Figure) experimentally causes an increase in oxygen consumption and the disappearance of glycogen from liver and muscles. Barker (1946) gave rats doses of 10 mg. DNOC per g. bodyweight, and found that oxygen consumption was increased. Moreover, Barnes (1953) has shown that the injection of DNOC into rats caused an initial fall in liver glycogen which was followed by a progressive rise, so that after 24 hours the level was higher than in control animals. Judah (1951) showed that under the influence of the dinitrophenols the uptake of inorganic phosphate by respiring mitochondrial preparations is decreased, but the consumption of oxygen increases. It seems possible that a similar uncoupling mechanism is the basis of the salicylate effect, though no direct evidence of this is yet to hand.

Only m.-hydroxybenzoic acid (Figure) was found to exert an inhibitory effect. It is of interest to note that Rosenberg (1952) observed that the m.-configuration confirmed inhibitory properties on phenols and amines when he measured both the ^{131}I

uptake by the thyroid of rats and milk peroxidase activity. The significance of this association is obscure, but it is remarkable that such a small change in molecular configuration leads to opposed experimental results.

Summary

(1) The effect of certain hydroxybenzoic acids on the oxygen consumption of Wistar rats is reported.

(2) Salicylic acid was found to stimulate the oxygen consumption whilst m.-hydroxybenzoic acid depressed it. The remaining compounds were inactive.

(3) The salicylate results are discussed in the light of suggested modes of action of related compounds in rheumatic fever.

I am grateful to Professor N. F. Maclagan for his advice and criticism in the preparation of this paper, and to the Governors' Discretionary Fund of Westminster Hospital for defraying part of the cost of these experiments.

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Effets de certains acides hydroxybenzoïques sur la consommation d'oxygène par des rats de Wistar

RÉSUMÉ

(1) On présente un rapport sur l'effet de certains acides hydroxybenzoïques sur la consommation d'oxygène par des rats de Wistar.

(2) On trouva que l'acide salicylique stimule la consommation d'oxygène alors que l'acide m-hydroxybenzoïque l'abaisse. Les autres composés furent inactives.

(3) On discute ces résultats avec des salicylates à la lumière des modes d'action supposée des composés voisins sur le rhumatisme articulaire aigu.

Efectos de ciertos ácidos hidroxibenzóicos sobre la consunción de oxígeno por ratas de Wistar

SUMARIO

(1) Se informa sobre el efecto de ciertos ácidos hidroxibenzóicos sobre la consunción de oxígeno por ratas de Wistar.

(2) Se halló que el ácido salicílico estimula la consunción de oxígeno mientras que el ácido m-hidroxibenzóico la deprime. Los demás compuestos no fueron activos.

(3) Se discute los resultados con los salicilatos en la luz de los modos sugeridos de acción de los compuestos afines sobre el reumatismo poliarticular agudo.

IMPLANTATION OF PLACENTAL TISSUE IN PATIENTS WITH RHEUMATOID ARTHRITIS*†

PRELIMINARY REPORT

BY

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(RECEIVED FOR PUBLICATION OCTOBER 23, 1953)

Many factors have an influence on rheumatoid arthritis. Since 1938 the favourable effect of pregnancy in most instances of this disease has been accepted (Hench, 1938). Subsequent to this observation, preparations associated with pregnancy have been employed for the treatment of rheumatoid arthritis with indifferent success. In recent years rheumatoid arthritis has been treated with transfusions of blood from pregnant women (Barsi, 1947; Watson, 1953), with serum from placental blood (Tufts, 1953; Aronson and others, 1952), and with postpartum plasma (Granirer, 1951; Neustadt and others, 1953), and conflicting reports as to the efficacy of these methods have been published.

Filatov (1944, 1945, 1946), the Russian ophthalmologist, has written extensively on the use of tissue implants. Though primarily concerned with diseases of the eye, he reported its use in many conditions, including arthritis.

Following these reports, a considerable interest in this form of therapy was shown in various parts of Europe (Tinozzi and others, 1951; Pflüger, 1952; Armand and Couadeau, 1950). A rather extensive literature exists on the treatment of retinitis pigmentosa with placental implantation; as one might expect, there is a marked variance in the reported results of the different investigators. Other workers cited the use of tissues, including placenta, in diseases in which the eye was not primarily involved. Thyroid gland implantation in a large series of patients with arthritis has been reported from Vienna (Mandl and Gyri, 1952), and from Paris (Etienne-Martin and others, 1952). Workers in Sweden (Edström and Thune, 1951) and Denmark (Wassmann, 1952) have implanted the anterior lobes of pituitary glands of pigs or calves in patients with rheumatoid arthritis with interesting results.

Material

Thirty-five patients with rheumatoid arthritis, classified according to the criteria of the American Rheumatism Association (Steinbrocker and others, 1949), were studied. The patients were taken at random and included twelve males and 23 females, varying in age from 22 years to 70 years. In six patients the disease had been present for periods of 3 months to 2 years, in five patients from 3 to 5 years, and in the remaining 24 patients from 6 to 50 years. With few exceptions the patients had previously received various forms of therapy, including gold salts and cortisone. In four patients the disease was classified‡ Stage II, in twenty Stage III, and in eleven Stage IV. The functional capacity was Class II in ten, Class III in eighteen, and Class IV in seven (Table I). The *x*-ray findings in each case were consistent with the stage of the disease, and in all but two patients the erythrocyte sedimentation rate was elevated.

TABLE I
PATIENTS CLASSIFIED ACCORDING TO SEVERITY OF RHEUMATOID PROCESS AND CLASS OF FUNCTIONAL CAPACITY

Class	Stage				
	I	II	III	IV	Total
I	—	—	—	—	—
II	—	1	7	2	10
III	—	1	11	6	18
IV	—	2	2	3	7
Total ..	—	4	20	11	35

‡ Severity of disease classified in four stages according to clinical and radiological changes: Stage I early; Stage II moderate; Stage III severe; Stage IV terminal status with ankylosis.

Functional impairment shown in four classes: Class I, all usual duties without handicap; Class II, normal activities despite discomfort or limited motion; Class III, few duties of usual occupation or self care; Class IV, largely or wholly incapacitated.

Response of rheumatoid activity to therapy, based entirely on objective findings, given in four grades: Grade I, complete remission; Grade II, major improvement; Grade III, minor improvement; Grade IV, no improvement.

* Read at the meeting of the American Rheumatism Association, May 29, 1953.

† This study was aided by a grant from the New York Chapter of the Arthritis and Rheumatism Foundation.

Method

Placental tissue not more than 24 hours old was obtained from women who gave a negative history for jaundice and in whom the history and serological tests for syphilis were negative. About 25 g. of tissue (the equivalent of a 2-cm. cube) was cut into small pieces. The material was immersed in a 1 per cent. aqueous solution of Brilliant Green for 1 hour, this tissue becoming permeated with the dye. The excess solution was poured off and the tissue was thoroughly rinsed a number of times with sterile distilled water in order to remove some of the remaining dye. Placental tissue prepared in this manner was sterile on incubation in broth and on agar media.

Under local procaine hydrochloride anaesthesia, an incision about 10 cm. long was made on the lateral aspect of the thigh through the subcutaneous fat down to the fascia and a pocket was made by undermining the fat. The small pieces of treated placenta were placed in the pocket and the incision closed with sutures. The patients were maintained on antibiotics for 4 to 7 days.

There were no unfavourable systemic reactions to the tissue implantation, but several patients had a slight elevation of temperature attributable to the procedure. The incisions did not heal by primary union and the wounds drained liquified material for a number of days and remained partially open for 3 to 5 weeks after the implant before healing by granulation. In one patient it was necessary to re-open the wound because it had closed without drainage.

Results

Of the 35 patients studied, fifteen showed no improvement (Grade IV), four were Grade III, sixteen Grade II, and none Grade I (Table II). Those who improved were aware of symptomatic improvement within a period of 2 to 10 days after the implant with increased mobility of some of the involved joints. Objective signs of improvement were manifested by decrease in heat, reduction in joint swelling, and improvement in range of motion. Both subjective and objective improvement were progressive over a period of 2 to 6 weeks, by which time the maximum benefits from the procedure usually were noted. The patients who were improved have maintained their improvement to date. This group includes two whose duration of improvement is 4 years, two 3½ years, and one more than 3 years. The remainder show a duration of improvement ranging from 2 to 10 months. This difference in time is due to the fact that the study was interrupted for a period of 2 years. With few exceptions, some decrease in sedimentation rate was noted in the Grade II patients following wound healing; this fall was not apparent immediately, but was noted over a period of from 4 to 12 weeks.

Case Reports

Case 2, 48-year-old white woman, gave a history of pain and swelling of fingers, wrists, elbows, knees, and

TABLE II
RESPONSE OF PATIENTS RECEIVING PLACENTAL IMPLANTATION

Case No.	Sex	Age	Duration of Disease (yrs)	Stage of Severity	Functional Class	Erythrocyte Sedimentation Rate	Date of Implant	Grade of Improvement
1	M	54	12	IV	III	90	18/6/49	III
*2	F	48	1	III	III	108	12/7/49	II
3	F	22	8	III	III	18	5/11/49	IV
4	F	62	19	IV	II	68	11/11/49	IV
5	F	45	1½	II	IV	59	12/11/49	IV
6	F	37	7	IV	IV	92	12/11/49	IV
7	M	70	3/12	II	II	66	22/11/49	II
8	M	34	1	IV	IV	12	29/12/49	II
9	M	63	8/12	III	III	104	21/3/50	II
10	M	51	12	III	IV	88	2/6/50	IV
11	M	46	21	III	IV	48	14/8/52	II
12	F	40	1	II	III	32	14/8/52	IV
13	F	58	5	III	III	48	29/9/52	IV
14	F	36	20	IV	III	61	31/10/52	III
15	F	30	8	IV	II	30	31/10/52	II
*16	M	46	2	II	IV	88	31/10/52	IV
17	F	39	3	III	III	61	28/11/52	II
18	M	51	16	III	II	58	12/12/52	IV
19	F	53	10	III	II	54	12/12/52	II
20	F	46	3½	III	III	64	27/1/53	II
21	F	63	35	III	III	102	27/1/53	III
22	M	26	10	III	III	73	6/2/53	IV
23	M	40	7	III	II	42	6/2/53	II
24	F	33	7½	III	III	35	20/2/53	IV
25	F	40	7	IV	III	57	13/3/53	II
26	F	66	50	IV	III	60	20/3/53	IV
27	F	30	18	III	II	37	20/3/53	II
28	F	62	5	III	III	35	27/3/53	II
29	M	35	24	III	IV	72	27/3/53	IV
30	F	48	12	IV	IV	92	3/4/53	II
31	F	45	10	IV	III	82	3/4/53	IV
32	F	35	5	IV	III	51	10/4/53	II
33	F	51	11	III	II	94	10/4/53	III
*34	F	37	15	III	II	34	17/4/53	II
35	M	64	19	III	III	95	17/4/53	IV

* See Text.

ankles of 1 year's duration. The shoulders and hips were also painful on motion. The pain had become progressively worse, so that sitting down or rising from a chair was done with extreme difficulty. She managed to descend a flight of steps by walking slowly backwards.

Examination revealed warm, swollen, tender knees that were painful on motion. The ankles were similarly involved. Motion of both shoulders and elbows was limited because of pain. The wrists were swollen and tender, and limited motion produced pain. The metacarpal-phalangeal joints and the proximal inter-phalangeal joints were swollen, warm, and tender; flexion of the fingers was incomplete. The erythrocyte sedimentation rate (Westergren) was 108 mm. in 1 hour. The rheumatoid arthritis was classified as Stage III, Class III.

Placental tissue implantation was done on July 12, 1949; 2 days later there was decrease in swelling of all involved joints except the right ankle, motion of the joints was less painful, and the range of motion was improved. Improvement was progressive over a period of 2 weeks and has been maintained to date. The therapeutic result was classified as Grade II.

Case 16, 46-year-old white man, gave a history of complete invalidism for 2 years because of arthritis. All the peripheral joints were actively involved, but the *x* ray revealed only minimal cartilage destruction. The erythrocyte sedimentation rate was 88 mm. in 1 hour. His rheumatoid arthritis was classified Stage II, Class IV.

He had been placed on oral cortisone with a daily maintenance dose of 100 mg., and on this regimen was free from all joint pain and interested in finding a job. When cortisone was withdrawn after a gradual reduction in dosage, all the symptoms returned and the objective findings were comparable to those present before cortisone.

Gelfoam, prepared in the manner described for placenta, was then implanted with no change in the patient's condition. Thyroid gland tissue similarly treated was then employed and no improvement was noted. Placental implantation was carried out, and 3 days after the implant the patient stated that he felt comfortable. On the 4th day he stated that he was free of all pain. On examination there was decrease in swelling of the involved joints, and a complete range of motion of all joints without pain; stairs were negotiated in a normal manner. This clinical remission lasted for 9 days, after which there was a sudden relapse and the patient rapidly reached his pre-treatment status. A second and third placental implantation were without benefit. With the fourth placental implant, the patient experienced a clinical remission similar to that following the first, but again the remission was short-lived, lasting only 9 days. The therapeutic result was classified as Grade IV because of the relapse. This case is reported in detail because of the significant, although short-lived, improvement.

Case 34, 37-year-old white woman, had had rheumatoid arthritis for 15 years. Gold salts therapy had been instituted 6 years ago, but had been stopped because of the occurrence of exfoliative dermatitis. The patient had significant relief of symptoms for a 2-year period while on cortisone, but it had become necessary to stop this medication because of significant oedema. Butazolidin was also effective but was discontinued because of the occurrence of a duodenal ulcer. Her arthritis then became progressively worse, so that in an effort to relieve pain she was taking Demerol several times a day in addition to aspirin and codein.

At the time of examination the fingers, wrists, elbows, shoulders, knees, ankles, toes, and jaw showed changes characteristic of advanced rheumatoid arthritis, and the erythrocyte sedimentation rate (Westergren) was 34 mm. in 1 hour. The disease was classified as Stage III, Class II.

Placental implantation was carried out on April 17, 1953. The patient noted subjective improvement 3 days later, and was able to get out of a chair and out of bed with greater ease without analgesics. There was decreased swelling and tenderness of the involved joints. Subjective and objective improvement continued over a period of 2 weeks and the improvement has been maintained to date. The therapeutic response is classified as Grade II.

Discussion

Experimental evidence indicates that ACTH (Opsahl and Long, 1951), gonadotropin and oestrogens (Stewart, 1951) are secreted by the placenta. Progesterone can be extracted from the placenta, but evidence of its secretion by this tissue is inconclusive. It seems most unlikely that any of the material that was implanted in this group of patients was active after the wound healed. The reason for this assumption is the discharge of liquified material which occurred before wound closure. Filatov believed that there was no hormonal action induced by this procedure, but thought that any beneficial effect that might be obtained was due to the elaboration of disintegration substances which he termed "catalysts" or enzymes. However, this does not preclude the possibility of some short-lived initial hormonal stimulus from the implanted material. Hench (1949) has stated that the activity of rheumatoid arthritis, "a basic biochemical disturbance of unknown type", is potentially reversible at any stage. He points out that although the pathological anatomy is largely irreversible, the pathologic physiology may be reversed. He suggests that powerful corrective forces lie dormant awaiting proper stimulation.

Summary

A preliminary series of observations in the use of placental tissue implants in rheumatoid arthritis is presented. In a group of 35 patients with rheumatoid arthritis, there was evidence of Grade II improvement in sixteen patients following subcutaneous implantation of human placental tissue; this

improvement has been maintained until the present time. The mode of action of this procedure is not known, but it is not considered to be due to any sustained hormonal elaboration by the implanted placenta. Many factors are known to influence favourably the course of rheumatoid arthritis, *e.g.* surgery, placebos, injection of inert materials, the natural course of the disease, the enthusiasm of the physician, and the will of the patient to get well. Psychological stimuli must be eliminated in assessing the value of any new procedure. With these reservations, the method may be investigated further to assess its relative significance in the treatment of rheumatoid arthritis.

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Greffe de tissu placentaire chez des malades atteints d'arthrite rhumatismale

RÉSUMÉ

On présente une série préliminaire d'observations sur l'emploi de greffes de tissu placentaire dans l'arthrite rhumatismale. Sur 35 malades atteints d'arthrite rhumatismale, 16 présentèrent des signes d'amélioration du 2-ème degré après une greffe souscutanée de tissu placentaire humain; cette amélioration se maintient toujours. On ne connaît pas le mode d'action de ce procédé et on ne croit pas qu'il s'agisse d'une élaboration hormonale soutenue des greffes placentaires. On connaît beaucoup de facteurs qui influencent favorablement l'évolution de l'arthrite rhumatismale, tels que remèdes factices, injections de produits inertes, interventions chirurgicales, évolution naturelle de la maladie, enthousiasme du médecin et volonté de guérir du malade. En déterminant la valeur de tout procédé nouveau il faut éliminer l'incitation psychologique. A ces restrictions près, cette méthode mérite des recherches ultérieures afin d'évaluer son importance relative dans le traitement de l'arthrite rhumatismale.

Injerto de tejido placentario en enfermos con artritis reumatoide

SUMARIO

Se presenta una serie preliminar de observaciones sobre injertos de tejido placentario en la artritis reumatoide. En un grupo de 35 enfermos con artritis reumatoide, 16 presentaron signos de mejoría de grado II después del injerto subcutáneo de tejido placentario humano; esta mejoría se mantiene todavía. No se conoce el modo de acción de este procedimiento y no se cree que se tratase de una elaboración hormonal sostenida de los injertos placentarios. Se conocen muchos factores que ejercen un efecto favorable en el curso de la artritis reumatoide, tales que cirugía, remedios facticios, inyecciones de productos inertos, evolución natural de la enfermedad, entusiasmo del médico y la voluntad de mejorar del enfermo. Al determinar el valor de un procedimiento nuevo hay que eliminar la estimulación psicológica. Con estas reservas, el método merece investigación ulterior para avaluar su importancia relativa en el tratamiento de la artritis reumatoide.

17-KETOSTEROID EXCRETION IN TWO UNUSUAL FORMS OF RHEUMATOID DISEASE

BY

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(RECEIVED FOR PUBLICATION NOVEMBER 19, 1953)

Davison, Koets, and Kuzell (1947, 1949) found an abnormally high average urinary excretion of 17-ketosteroids in thirteen male patients with ankylosing spondylitis. In some cases, radiotherapy restored the excretion to normal. These results appeared worthy of further investigation. The urinary 17-ketosteroid excretion of a number of patients with ankylosing spondylitis and Sjögren's syndrome, in which rheumatoid manifestations are a common feature, has therefore been measured.

Experiments

Total neutral 17-ketosteroid estimations were carried out on 24-hr urine samples of eleven female patients with Sjögren's disease, and one female and five male patients with ankylosing spondylitis, all before treatment, or during an exacerbation of the disease. The method of analysis was similar to that recommended by the M.R.C. committee for clinical endocrinology. In three patients with Sjögren's syndrome and five with ankylosing spondylitis, the quantitative composition of the 17-ketosteroids was determined by separation into eight main fractions by adsorption chromatography (Pond, 1951).

Results

The results of the total 17-ketosteroid assays are shown in Table I. The detailed results of the fractionation of the 17-ketosteroid extracts have been published elsewhere (Pond, 1953a) and summaries of the main findings are presented in Table II.

TABLE I
TOTAL NEUTRAL 17-KETOSTEROID VALUES
(mg./24 hrs excreted, corrected nearest whole number)

Type of Rheumatic Disease	Case No.	Sex	Age (yrs)	Total 17-ketosteroids (mg.)
Sjögren's Syndrome	1	F	54	2
	2	F	47	2
	3	F	36	3
	4	F	54	3
	5	F	71	3
	6	F	51	2
	7	F	52	3
	8	F	53	3
	9	F	64	1
	10	F	49	2
	11	F	62	2
	11 total	F	54 average	2·3* average
Ankylosing Spondylitis	1	M	42	9
	2	M	29	6
	3	M	26	12
	4	M	27	5
	5	F	41	7
	6	M	33	10
	6 total	5 M 1 F	33 average	8·2* average

* Normal ranges for this laboratory: Male 6-18 mg./24 hrs. Female 4-14 mg./24 hrs.

TABLE II
FRACTIONATION OF 17-KETOSTEROIDS
(mg./24 hrs unless stated)

Category	Average Age (yrs)	Sex	Total 17-ketosteroids		Fractions I, II, III β fraction				Fraction IV Androsterone				Fraction V Etiocholanolone				Fractions VI and VII 11 β hydroxy 17-ketosteroids			
			Range	Average	Range		Average		Range		Average		Range		Average		Range		Average	
					No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Normal	27	M	7-18	12	1·1-4·9	14-36	2·5	21	2·4-6·3	28-48	4·3	36	1·9-6·1	24-41	3·6	30	0·8 - 1·6	7-15	1·2	10
Normal	25	F	4-14	8	0·6-2·9	12-26	1·6	20	1·1-5·2	24-43	2·5	31	1·2-5·3	30-42	2·9	35	0·5-1·0	5-16	0·7	9
Sjögren's Disease	54	F	1-3	2·3	0·1-0·3	8-13	0·2	9	0·3-1·0	15-31	0·6	26	0·3-1·9	25-48	1·0	44	0·3-0·8	19-25	0·5	21
Ankylosing Spondylitis	33	5 M 1 F	5-12	8·2	0·8-4·6	17-38	2·1	27	1·1-4·3	20-43	2·4	21	2·0-3·9	29-44	2·7	35	0·3-0·7	4-9	0·6	8

All the total 17-ketosteroid estimations in patients with Sjögren's syndrome gave results of between 1 and 3 mg./24 hrs (average 2·3 mg., *i.e.* below the lower limit of normal for women for this laboratory) (see Table I). In contrast, the results in the patients with ankylosing spondylitis were all within normal limits. None approached the upper limit of the normal range as suggested by the work of Davison and others (1947), but on the contrary, some approached the lower limit of normality.

Fractionation of the 17-ketosteroid extracts showed the following trends in steroid excretion in these two types of patient:

The patients with Sjögren's disease showed a lowering of all fractions and in particular a lowering of the β fraction, which is generally considered to be an indication of adrenocortical activity.

The 11-oxy-17-ketosteroid fraction (a probable breakdown product of the adrenal glucocorticoids) was rather low in one patient, but within normal limits in the other two.

One patient showed a relatively raised etiocholanolone excretion, which has been found by other workers to be characteristic of patients with debilitating or malignant disease (Robinson and Goulden, 1949). Etiocholanolone is a non-androgenic isomer of androsterone, and the two fractions normally constitute two-thirds of the total 17-ketosteroids. A rise of this fraction is not necessarily of endocrinological significance.

The fractionation patterns of patients with ankylosing spondylitis were within normal limits with few exceptions: one patient showed an unusually high β fraction, for which no apparent explanation could be found; one showed a high value for etiocholanolone, probably suggestive of general debility as previously described; only one showed any significant lowering of the 11-oxy-17-ketosteroid fraction, though all were below the mean for normal men.

Discussion

It is interesting that the excretion of 17-ketosteroids was consistently lowered in all patients with Sjögren's disease. The only other case of Sjögren's disease, in which 17-ketosteroid assay has been recorded in the literature, had a normal value (Frenkel, Hellinga, and Groen, 1951). The low values here may, in part, be due to the advanced ages of these patients, though three of them were under 50 years (36-71 years, average 54). It is also possible that the difficulties of mastication experienced by many of them, may lead to under-nourishment, which will in itself lower 17-ketosteroid excretion. Fractionation studies failed to throw much light on the cause of the low 17-ketosteroid values. The 11-oxy-17-ketosteroids, which are probably metabolic end-products of the adrenal cortical hormone functions, were mainly within normal limits. The low β fraction suggested a deficiency in the production of other important steroids of the adrenal cortex. The significance of the excretion of these various steroids is more fully discussed elsewhere (Pond, 1954). The conclusion is that the results of 17-ketosteroid studies do not indicate any endocrine abnormality in Sjögren's disease; they reflect the debilitating nature of the disease, but suggest a potentially normal adrenocortical function.

The results of Davison and others (1947) in ankylosing spondylitis cannot be confirmed. Three of those cases were complicated by other conditions, anaemia, pulmonary tuberculosis, and muscular dystrophy, which might lower the 17-ketosteroid output, but no explanation can be offered for the consistent failure to find high values. Fractionation of the 17-ketosteroids showed no abnormality of the type of steroid excreted with the exception of one rather high β fraction. No explanation can be offered for this, but it has also been found occasionally in normal men. One patient showed changes reflecting the debilitating nature of the disease, as in Sjögren's patients. Again, there is no suggestion that these patients have any endocrine abnormality of androgen function, although adrenocortical activity as represented by excretion of the 11-β-hydroxy 17-ketosteroids seems to be slightly below the average. This may be associated with a low adrenal corticoid excretion, which is interesting, since these patients often respond well to cortisone.

Summary

Patients with Sjögren's disease and ankylosing spondylitis were studied for abnormality of the 17-ketosteroid excretion, both by total 24-hr urinary assays and by fractionation studies on the urinary extracts. The patients with Sjögren's disease show consistently lowered total urinary 17-ketosteroid values, possible reasons for which are discussed. In other respects little abnormality of 17-ketosteroid excretion was found, and there was no suggestion of any endocrine basis for the disease. Similarly, little abnormality could be found in the patients with ankylosing spondylitis in this respect, and the results of previous workers, who found a raised 17-ketosteroid excretion in many patients of this type, were not confirmed.

I wish to thank Professor C. H. Gray for facilities for these experiments and for advice and encouragement throughout; the physicians of King's College Hospital,

especially Dr. R. S. Bruce Pearson, for their co-operation in the loan of suitable patients; and Miss Jane Cowan for technical assistance.

The work was carried out during the tenure of a William Gibson research scholarship for medical women, and I am also indebted to the governors of King's College Hospital for a grant from the endowment fund.

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Excrétion des 17-cetosteroïdes dans deux formes rares de la maladie rhumatismale

RÉSUMÉ

L'auteur étudia dans la maladie de Sjögren et dans la spondylarthrite ankylosante l'excrétion urinaire totale par 24 heures des 17-cetostéroïdes et en détermina les fractions au moyen de l'analyse chromatographique. Dans la maladie de Sjögren il trouva constamment le taux diminué, mais ne constata aucune autre anomalie des 17-cetostéroïdes. Il ne pense pas que cela prouve l'origine endocrine de la maladie et il explique la diminution quantitative par des facteurs autres que le processus morbide. L'excrétion des 17-cetostéroïdes était aussi normale dans la spondylarthrite ankylosante, contrairement aux résultats des autres auteurs qui l'avaient trouvé augmentée dans cette maladie.

Excreción de 17-cetoesteroides en dos formas raras de la enfermedad reumática

SUMARIO

El autor estudió en la enfermedad de Sjögren y en la espondilitis anquilosante la excreción urinaria total por 24 horas de 17-cetosteroides y determinó las fracciones de éstos por medio de analisis cromatográfica. En la enfermedad de Sjögren hubo disminución constante de la tasa, pero ninguna otra anomalía de los 17-cetosteroides. La base endocrina de la enfermedad no se ve, pues, comprobada y el autor sugiere otras causas de la baja excretoria. La excreción de 17-cetosteroides fué también normal en la espondilitis anquilosante, contrariamente a los resultados de otros autores que la hallaron aumentada en esta enfermedad.

CORRESPONDENCE

To the Editors of the
Annals of the Rheumatic Diseases.

DEAR SIRS,—Reports have appeared of an agent, Trafuril Ointment (Ciba), containing 5 per cent. by weight of a rubefacient, tetra-hydrofurfuryl nicotinic acid ester, which describe its use as a diagnostic skin test for rheumatoid arthritis. When a small amount of this material is rubbed into the skin of a normal subject a mild local erythema (typical response) results. An absence of erythema is considered to be abnormal (atypical response).

Nassim and Banner (1952) reported that no reaction occurred when the ointment was rubbed on the skin of five patients with rheumatoid arthritis, but that when it was rubbed on the skin of patients with tuberculous arthritis and osteo-arthritis, a typical reaction (local erythema) resulted in about 15 minutes. They also found that the atypical reaction became typical in arthritic patients after they had received gold salts or large doses of ACTH or cortisone.

Oka (1953) reported on the use of this test in an extensive series of patients; he found a correlation between the test and the erythrocyte sedimentation rate.

We have studied a group of patients and normal subjects, and our results differ in some respects, though they corroborate some of the findings of the above investigators. The following chart is a summary of our results. We did not distinguish between slight and strong typical responses, as we considered the atypical response (no erythema) the important result to look for.

Our results may be summarized as follows: we found that only 20 per cent. of patients having rheumatoid arthritis gave an atypical response, whereas, Oka reported 68 per cent. We found that 4 per cent. of normal subjects gave an atypical response, whereas Oka reports that none gave such an atypical response. There is no correlation in our series between the response and the erythrocyte sedimentation rate. There is some variation in the response of individual patients when the test is repeated from time to time. Thus, one patient with osteo-arthritis gave a typical response on one occasion and an atypical response 5 weeks later. This patient had a marked psychic component. It is also interesting to note that of four cases of psychogenic rheumatism, three gave an atypical response.

Our conclusion is that this skin test when atypical, may corroborate a diagnosis of rheumatoid arthritis, but that a typical response does not exclude it.

Yours faithfully,

HARRY BARTFELD and EDWARD F. HARTUNG,

580 Park Avenue,
New York City, U.S.A.
October 5, 1953.

Investigator	Bartfeld and Hartung (1953)			Oka (1953)			
Disease	No. of Cases	Response (%)		No. of Cases	Response (%)		
		Atypical	Typical		Atypical	Typical	
						Slight	Strong
Rheumatoid Arthritis	40	20	80	228	68	22	11
Ankylosing Spondylitis	4	50	50	16	75	12·5	12·5
Gout and Gouty Arthritis	3	0	100				
Osteo-arthritis	50	2	98				
Fibrositis and Bursitis	9	0	100				
Psychogenic Rheumatism	4	75	25				
Normal Controls	30	4	96	69	0	5·8	94·2

BOOK REVIEW

Rheumatic Diseases. By Eugene F. Traut. 1952. Pp. 942. Mosby, St. Louis, U.S.A.

The preface of this book on rheumatic diseases explains that so wide a subject cannot be a "compilation of the discoveries of the author", but must "attempt to assemble material accepted as factual by current authorities". "It must also contain controversial subject matter."

We are promised that currently-used treatment will be "considered critically and even with the prejudice born of personal experience". This promise is redeemed frequently throughout the book.

The author presents an uncompromising condemnation of gold as a therapeutic agent in the treatment of rheumatoid arthritis. He feels that the heyday of chrysotherapy has passed, that enthusiasm for its exhibition is waning, and that it is questionable whether its use is worthy of extensive consideration. Emphasizing the toxic reactions he says:

> "In general the less gold given the less the likelihood of poisoning. (This could be reduced to nil by abstaining from gold)."

The "prejudice born of personal experience" which makes the author discountenance gold so whole-heartedly would seem to be at work again in his considered support of the value of vaccine therapy. Certain it is that, were he presenting material "accepted as factual by current authorities", those authorities would subscribe overwhelmingly to the opinion that the heyday of vaccine therapy had passed, that enthusiasm for its exhibition had already waned, and that it was questionable whether its use was worthy of extensive consideration.

Throughout the book, interesting clinical experiences are cited in support of this or that contention, but nowadays clinical impressions require to be supported by concrete observations and "factual findings".

There are interesting chapters on "Symptoms, Findings and Diagnosis of Joint Disease" and on "Rheumatic Diseases of the Back"—to mention only two. There is an unusual chapter on joint deformity in immobilized extremities secondary to neurological disturbance or "fixation apparatus". Selected contributors present special chapters on the psychological factors in rheumatoid arthritis, the collagen diseases, the skin, ocular manifestations, roentgen therapy, the prevention of deformity, and the surgery of arthritis. The section on "Histopathology of Muscle in Rheumatoid Arthritis and Other Diseases" has been written by the author in collaboration with a colleague.

The large number of acknowledgements tends to mask the fact that the author would seem to have contributed 754 pages of the text out of a total of 896 pages (and will no doubt have been responsible for most of the 46 pages of an excellent index). It is obvious that he has contributed much more to the book which bears his name than is often the case in this type of publication.

He has attempted to arrange the book so that the aetiology of joint diseases *as a whole* is dealt with in one section. Similarly, the general symptoms and general treatment of joint diseases are presented in separate sections. In these sections attention is called to the special features or requirements for specific conditions where they differ from the general principles laid down. The object of this was to avoid repetition, but despite this laudable object (and how tiresome the repetition of so many of these modern "edited" books can be), there is still a good deal of reiteration throughout the book—some of it inevitable.

The book is well produced with many good illustrations and charts, and the printing is excellent.

J. W. T. PATTERSON.

FIRST CHAIR OF RHEUMATOLOGY IN BRAZIL

A professorship in rheumatology has been founded at the Post-Graduate School of Medicine of the University of Brazil. Dr. Jacques Houli has been elected as the first professor, and the first regular course will be held during 1954.

BRITISH RHEUMATIC ASSOCIATION

The sixth Annual General Meeting was held on October 27, 1953, under the chairmanship of the Rt. Hon. Tom Williams, M.P. Reports were presented of a year's useful work in promoting the welfare of rheumatic sufferers and assisting the disabled to find occupation and employment. Further particulars of the society and its work may be had from the Secretary, 11 Beaumont Street, London, W.1.

HEBERDEN SOCIETY

ANNUAL REPORT, 1953

The attendances at the Society's meetings during 1953, and the quality of the papers presented, maintained as high a standard as in the previous year. It is with deep regret that the death is recorded of Dr. Mervyn H. Gordon, an Honorary Member of the Society whose wise counsel and guidance will be greatly missed. Mr. Charles Gray, Mr. C. Hamblen-Thomas, Dr. George Crosby, and Dr. M. H. L. Desmarais have resigned, and the following new members have been elected:

Ordinary Members: Drs J. H. H. Glyn, B. Cruickshank, Ronald Harris, R. R. H. Lovell, and K. A. Latter;

Associate Members: Drs J. H. Jacobs, M. L. Joule, J. E. Dawson, G. O. Storey, P. O. Williams, and J. Sharp.

The society looks forward to a renewal of its financial "Grant-in-Aid" from the Empire Rheumatism Council, without which it might become necessary to curtail some of the society's educational work.

Activities.—The first clinical meeting of 1953 took place at the Middlesex Hospital on April 10, by kind permission of the Dean of the Medical School. Papers were presented by Prof. A. Kekwick, and Drs A. E. Kellie, A. A. Snaith and A. P. Wade, B. B. Jacobs, D. K. Ford and P. O. Williams (*Annals*, 1953, **12**, 239).

A clinical meeting was held at 11 Chandos Street, W.1, on May 15, at which papers were presented by Prof. J. H. Kellgren and Prof. A. Bradford Hill (Dr. J. J. R. Duthie deputizing), and Dr. H. F. West; Mr. J. P. Arden showed a film on "Judet Arthroplasty in Still's Disease" (*Annals*, 1953, **12**, 239).

The Heberden Round was held on July 10 and 11 in Manchester and Buxton. The Manchester meeting took place in the new Clinical Sciences Building of the University of Manchester, where Professor Kellgren illustrated types of osteo-arthritis, and demonstrations were given by Drs J. Ball, H. G. B. Slack, and D. S. Jackson in the Rheumatism Research Laboratories. At the Royal Devonshire Hospital, Buxton, Drs J. C. Cregan, R. Harris, and H. S. Barber presented papers (*Annals*, 1953, **12**, 239).

A clinical meeting, organized by Dr. Hugh Burt of the Department of Physical Medicine, was held at University College Hospital, London, on October 23, at which cases were demonstrated, and papers were presented by Professor M. L. Rosenheim and Dr. J. Anderson, Drs C. E. Dent and B. Senior, Drs H. Burt and S. Mattingley, and Drs W. D. Fletcher and D. A. Kininmonth. The meeting concluded with an amusing and instructive diagnostic quiz (*Annals*, 1953, **12**, 359).

After the annual general meeting, held on December 5 at the Royal College of Surgeons, papers were presented by Drs F. J. Bach and A. Freedman (*London*), Dr. H. F. West (*Sheffield*), Dr. J. Sharp (*Manchester*), Dr. M. Thompson (introduced by Dr. J. J. R. Duthie, *Edinburgh*), and Dr. P. W. Darby (introduced by Prof. N. F. Maclagan, *London*) (*Annals*, 1953, **12**, 359).

The Heberden Oration for 1953 was delivered by Sir Russell Brain, P.R.C.P., at the Royal College of Surgeons, on December 4, on "Spondylosis: the Known and the Unknown", and the Heberden Medal was presented to the orator by the President of the Society.

The annual dinner was held on December 4 at the Royal College of Surgeons: among the guests of honour were the Home Secretary, the Rt. Hon. Sir David Maxwell Fyfe, Q.C., M.P., Miss Patricia Hornsby-Smith, M.P., Parliamentary Secretary to the Ministry of Health; the President of the Royal College of Physicians, Sir W. Russell Brain, who was accompanied by Lady Brain; the Chief Medical Officer, Ministry of Health, Sir John Charles; Sir Reginald Watson-Jones, Vice-President of the Royal College of Surgeons; and the editors of the *British Medical Journal* and the *Lancet*.

Library.—The Society's library, which is housed at the Ciba Foundation, 41 Portland Place, W.1, by kind permission of the Trustees, has received the following additions during the year:

Presented by the Apothecaries' Society:

KINGLAKE, R.	A Dissertation on Gout, 1804.
BLACKMORE, R.	Discourse on the Gout, Rheumatism and the King's Evil (2nd edition), 1735.
PARKINSON	Observations on Nature and Cure of Gout, 1805.
GAIRDNER	Gout: Its History, its Cause and its Cure, 1849.
TENNISON, R.	Essay on Nature of Gout, 1724.

Presented by the Royal College of Surgeons:

HEBERDEN, W.	An Essay on Mithridatium and Theriaca, 1745.

Presented by Dr. R. M. Mason:

CULLEN, W.	First Lines on Practice of Physic, Vol. 1, 1802.

Presented by the Hon. Librarian, Dr. W. S. C. Copeman:

ANON.	Laugh and Lye Down: A Pleasant Remedy for the Gout: poem, 1739.
DAWSON, T.	Cases in Acute Rheumatism and the Gout (4th edition), 1776.
LA BEAUME, M.	Cases of Indigestion, Gout, etc., cured by Galvanism (2nd edition), 1827.
CHEYNE, G.	An Essay of the True Nature and Method of treating the Gout (6th edition), 1724.
ELLWANGER, G. H.	Meditations on Gout, 1897.
FALCONER, W.	Observations on Dr. Cadogan's Dissertation on the Gout, 1772.
PALMER, W.	Dissertation Medica inauguralis de Podagra, 1830.

Deposited on permanent loan by the Royal National Hospital for Rheumatic Diseases, Bath:

	Atlas of Illustrations of Pathology—Gout and Rheumatism. Compiled for New Sydenham Society, 1900.
EWART, W.	Gout and Goutiness, 1896.
BRUCE, W.	Sciatica, 1913.
BEAUMONT, W. M.	Rheumatic Iritis and other Reprints, 1914.
LANE, H.	Differentiation in Rheumatic Diseases, 1892.
CADOGAN, W.	Essay on Gout (reprint), John Ruhrah, 1925.
SYMES, J. O.	The Rheumatic Diseases, 1905.
——	Treatment of Rheumatic Infections, published by Parke, Davis & Co., 1913.
JONES, R. L.	Arthritis Deformans, comprising Rheumatoid Arthritis, Osteoarthritis and Spondylitis, 1909.
STOCKMAN, R.	Rheumatism and Arthritis, 1920.
——	Incidence of Rheumatic Diseases, M.O.H. Report, 1924.
GLOVER, J. A.	Report on Chronic Arthritis, 1928.
BIGG, H. H.	Orthopraxy—the Mechanical Treatment of Deformities, Debilities and Deficiencies of the Human Frame, 1869.
SCUDAMORE, C.	A Treatise on the Nature and Cure of Gout and Rheumatism, 1819.
FOAKES	Gout and Rheumatic Gout—a New Method of Cure, 1878.
HYDE, S.	The Causes and Treatment of Rheumatoid Arthritis, 1896.
CHARCOT, J. M.	Goute Rheumatisme, 1890.
POYNTON, F., and PAYNE, J.	Researches on Rheumatism, 1913.
SPENDER, J. K.	Osteoarthritis, 1889.
GARROD, SIR A.	Gout and Rheumatic Gout, 1876.
WILDE, P.	Rheumatism, Cause, Prevention and Cure, 1893.
FORSEBROOK, W. H. R.	Osteoarthritis, 1893.
DUCKWORTH, SIR D.	A Treatise on Gout, 1889.
STRANGEWAYS, T. S. P.	Rheumatoid Arthritis, 1905.
CADOGAN, W.	A Dissertation on the Gout, 1772.
ADAMS, R.	A Treatise on Rheumatic Gout, 1873.
LORTAT-JACOB, and SABAREANU, G.	Les Sciatiques, 1910.
LLEWELLYN, L. J.	Rheumatism and Gout, 1927.
BANNATYNE, G.	Rheumatoid Arthritis, 1906.
MACLAGAN, T. J.	Rheumatism—its Nature, Pathology and Treatment.
——	Rheumatism, Rheumatic Gout and Sciatica, 1860.
BANNATYNE, G.	Rheumatoid Arthritis, its Pathology, Morbid Anatomy and Treatment, 1896.
WARNER, F.	A full and plain account of Gout, 1768.
WILDE, P.	Gout, Rheumatism and Arthritis, 1921.
LUFF, A. P.	Gout—its Pathology and Treatment, 1898.
GRANVILLE, J. M.	Gout in its Clinical Aspects, 1885.
LINDSAY, J.	Gout, 1913.
ROOSE, R.	Gout and its relation to Diseases of the Liver and Kidneys, 1887.
LANE AND GRIFFITHS	The Rheumatic Diseases—So-called, 1890.
DUCKWORTH, D.	Gout, 1909.
——	Acta Rheumatologica, 1935-38.
——	Bulletin of the Committee for Study of Special Diseases, 1805.

Purchased by the Heberden Society from the President's Fund:

MARTEN, J.	A Treatise of the Gout (4th edition), 1738.
THOMPSON, T.	Historical and Critical Treatise of the Gout (2nd edition), 1752.
ANON.	A New System of the Gout and Rheumatism, 1717.

In accordance with the wishes of the Executive Committee, a full Catalogue of the Society's books is being prepared, and it is hoped to issue this with the next Annual Report.

It is much hoped that members will present to the library any books or items of rheumatological interest dating prior to 1914.

ARRANGEMENTS FOR 1954

May 7 and 8.—The Heberden Round will be held at Leeds and Harrogate.

October.—Clinical meeting at the Post-Graduate Medical School, Ducane Road, London, W.12.

December 3 and 4.—The Heberden Oration, annual general meeting, and annual dinner.

Titles and summaries of original communications which Members wish to make to the Society during 1954 should be sent to the Senior Hon. Secretary (Dr. G. R. Fearnley, Post-Graduate Medical School, Ducane Road,

London, W.12), together with an abstract not exceeding fifty words, at least one month before the date of meeting. Additional meetings will be arranged if necessary.

Abstracts of papers delivered are published in the *Annals of the Rheumatic Diseases.*

Officers for 1954

President	Professor R. E. Tunbridge
President-Elect	Dr. C. E. Fletcher
Hon. Treasurer	Dr. C. E. Fletcher
Senior Hon. Secretary	Dr. G. R. Fearnley
Junior Hon. Secretary	Dr. Alan G. S. Hill
Hon. Librarian	Dr. W. S. C. Copeman
Hon. Auditor	Wilfred G. Wilks

Executive Committee

Dr. F. Dudley Hart	Dr. Oswald Savage
Prof. J. H. Kellgren	Dr. W. S. Tegner
Mr. H. Osmond-Clarke	Dr. H. F. West

Clinical Meetings

The following papers were presented at a meeting held at the Royal College of Surgeons on December 5, 1953. Dr. J. Forestier (*Aix-les-Bains*) was present at the meeting and joined in the short discussions which followed each paper.

Drs F. J. Bach and A. Freedman (*London*): Mepacrin and Butazolidin in Rheumatoid Arthritis.

Dr. H. F. West (*Sheffield*): Purified ACTH Gel—Clinical and Chemical Assays in Rheumatoid Patients.*

Dr. J. Sharp (*Manchester*): Familial Vascular, Ligamentous, and Articular Calcification.†

Dr. M. Thompson (*Edinburgh*), introduced by Dr. J. J. R. Duthie : Osteitis Condensans Ilii and its Differentiation from Ankylosing Spondylitis.

Dr. P. W. Darby (*London*), introduced by Prof. N. F. Maclagan: Liver Function Tests in Rheumatoid Arthritis.

Professor R. E. Tunbridge took the chair at a meeting held on February 26, 1954, in the Meyerstein Theatre, Westminster Medical School.

Dr. Jacques Forestier showed a case of ankylosing spondylitis and the use of a supporting belt (originated by Dr. Loring T. Swaim, *Boston, Mass.*) which, while holding the spine upright, does not interfere with respiration. Before fitting the belt, Dr. Forestier described his routine treatment for correcting the kyphosis so common in these cases.

A case of Reiter's syndrome was shown by Lt.-Col. J. P. Baird, R.A.M.C. A sergeant, aged 36, with 18 years' service became extremely ill in the summer of 1953 with marked involvement of several joints, urethral discharge, and bilateral conjunctivitis. Keratodermia blenorrhagica developed a few weeks later. He was given cortisone by mouth, and although this discontinued when he developed pneumonia with a left pleural effusion in December, the improvement which had started on cortisone continued and his general condition was much improved.

Lt.-Col. R. J. G. Morrison, R.A.M.C., showed a patient, aged 21, with a peculiar congenital condition, several other members of whose family were similarly affected. His knees, elbows, and thumbs were congenitally abnormal, and he had, in addition, gross mediastinal widening and was receiving deep *x*-ray treatment for what was probably a lymphadenoma. His blood chemistry was normal; *x* rays showed a well-marked periosteal reaction with new bone formation around all the long bones, including the clavicles. The fingers were not clubbed. Dr. Philip Ellman and Dr. Dudley Hart considered this to be a case of hypertrophic pulmonary osteopathy, but Mr. Coltart felt that this diagnosis was not entirely satisfactory.

A case of rheumatoid arthritis with lung changes was shown by Dr. J. C. Leonard. This patient, who had previously been shown at a clinical meeting of the Heberden Society 4 years ago, had developed thyrotoxicosis in 1930 which had been treated with deep *x* rays. Rheumatoid arthritis commenced shortly after the war and at this time clubbing appeared in the fingers and *x* rays showed fine reticulosis in the lung fields. It had previously been suggested that this might be a rheumatoid manifestation, but since then the patient had developed complete laryngeal obstruction, and he now had a permanent tracheotomy. This late complication of irradiation was thought to be a more likely cause of the lung changes. Dr. Dudley Hart commented on the fact that thyroidectomized patients also sometimes develop clubbing.

A case of nodular rheumatoid arthritis with extensor sheath swellings in a woman of 49 was shown by Dr. F. Dudley Hart and Mr. J. P. Reidy. Dr. Hart commented on the frequency of extensor sheath swellings as a diagnostic physical sign in rheumatoid arthritis and also on the scanty information concerning them in the current textbooks. This patient had developed from time to time several dozen nodules ranging from 1 mm. to 3 in. across, and several had been excised with considerable relief of symptoms. Hydrocortisone had been injected into one extensor sheath swelling without effect.

Dr. J. G. Humble showed a case of rheumatoid arthritis with clotting defects on Butazolidin therapy, and suggested that in certain cases Butazolidin appeared to lower the prothrombin time of the blood. He stated that this defect could be rapidly corrected by giving vitamin K_1.

Dr. P. D. Samman showed a diabetic patient who had been receiving insulin for 23 years. Only in the last year had he noticed that his neck was getting larger so that he needed a larger size in collars. Examination showed thickening and hardening of the skin of the back of the neck, spreading down over the shoulders, the greater part of the chest, and the upper arms. Biopsy was made to a depth of $\frac{5}{8}$ in. without reaching the subcutaneous tissue. This thickening consisted of a very thin layer of epidermis, the remainder being a mass of collagen. Dr. Samman suggested that this was a peculiar case of scleroderma. Professor Tunbridge thought the condition was not connected with the diabetes in any way.

* See p. 56 of this issue.
† See p. 15 of this issue.

SOCIETÀ ITALIANA DI REUMATOLOGIA

Second Rome Rheumatology Day, 1954

The Centro di Reumatologia di Roma organized this meeting at the Istituto di Semeiotica Medica dell'Università di Roma on February 13 and 14, 1954. Professor T. Lucherini (*Rome*) took the chair at a large gathering which included representatives from universities, hospitals, and public health departments all over the country. The papers by Prof. Eric Martin (*Geneva*) on "The Early Diagnosis of Rheumatoid Arthritis", and Prof. A. Lunedi (*Florence*) on "Two Types of Rheumatism following Scarlet Fever" were followed by a lively discussion. Papers were also read by:

Drs J. Cahn, G. Georges, and R. Pierre (*Paris*): Comparison of the Anti-inflammatory Properties of Phenylbutazone and the Strontium Salts of L-ascorbic and 2-phenylquinolene-4-carbonic Acids.

Prof. T. Lucherini (*Rome*): Articular Manifestations and Gynaecomastia in Marie's Chronic Hypertrophic Osteopathy (Study of the Aetiopathogenic Problem).

Drs G. Casolo and C. A. Maggi (*Milan*): Serum Proteins in Rheumatoid Carditis.

Dr. A. Masturzo (*Naples*): Contributions to the Diagnosis and Therapy of Sciatica.

Drs M. Zacco, E. M. Richardson, J. O. Crittenden, F. C. Dohan, H. Bulashenko, and J. L. Hollander (*Philadelphia*): Cortisone and Hydrocortisone Injections in Rheumatoid Arthritis.

Drs A. Collicelli, L. Lai, and V. Puddu (*Rome*): Observations on Rheumatic Activity in relation to the Surgical Treatment of Mitral Stenosis.

Drs P. de Nicola and G. Curtarelli (*Pavia and Milan*): Cortisone and ACTH Treatment and Coagulation Factors.

Dr. G. Amatulli (*Milan*): Considerations of a Case of Dermatomyositis.

Drs F. Melloni, F. Porro, and B. Mancini (*Milan*): Disturbances in the Water Balance during Treatment with Phenylbutazone.

Dr. P. Preziosi (*Naples*): Antirheumatic Activity of the New Salicylic and Gentisic Derivatives.

Drs L. A. Scuro and L. Ortona (*Rome*): A New Type of Penicillin (N-N′-dibenzylethylenediamine dipenicillin) in the Prophylaxis of Rheumatic Diseases.

Dr. G. Piacentini (*Colleferro*): Specific Iconographic Aspects of the Hip Joints and the Skull observed during Tuberculous Meningitis.

Dr. E. Tosti (*Rome*): The Eye and Rheumatism.

Drs L. Motta and C. Sfogliano (*Catania*) gave six short papers on various laboratory tests in the diagnosis of rheumatism.

FELLOWSHIP OF POSTGRADUATE MEDICINE

Week-end Course in the Rheumatic Diseases

A concentrated course with clinical lectures, practical demonstrations, and ward rounds (including demonstrations of cases treated with ACTH and cortisone) is being held at the Rheumatism Unit, St. Stephen's Hospital, London, on March 27 and 28, 1954. Sir Adolphe Abrahams, O.B.E., F.R.C.P., will take the chair, and the programme will include the following:

Prof. S. J. Hartfall:	Inaugural Lecture: General Adaptation Theory of the Practice of Rheumatology.
Dr. Raymond Daley:	Rheumatic Fever and its Sequelae.
Dr. J. A. Purser:	Psychiatric Factors in the Chronic Rheumatic Diseases.
Dr. Francis Bach:	Management of the Rheumatic Patient, with ward round, and demonstration of methods of physical treatment and rehabilitation.
Dr. Gordon Signy:	Aetiology and Pathology of the Rheumatic Diseases.
Dr. F. Dudley Hart:	Ankylosing Spondylitis.
Mr. H. E. Harding:	Low Back Pain.
Dr. Philip Ellman:	Clinical Manifestations of "Rheumatoid Disease", with ward round and demonstration of cases.
Dr. Leon Cudkowicz:	Drug Therapy in the Rheumatic Diseases.
Dr. Frank Sargent:	Pain—Neuritic and Referred.
Dr. Grace Batten:	Radiological Diagnosis of the Rheumatic Diseases (lantern slides).

This course is open only to members of the Fellowship of Postgraduate Medicine, 60, Portland Place, W.1.

ABSTRACTS

This section of the ANNALS *is published in collaboration with the two abstracting Journals,* ABSTRACTS OF WORLD MEDICINE, *and* OPHTHALMIC LITERATURE, *published by the British Medical Association.*

The abstracts selected for this Journal are divided into the following sections: Acute Rheumatism; Chronic Articular Rheumatism (Rheumatoid Arthritis, Osteo-Arthritis, Spondylitis, Miscellaneous); Disk Syndrome; Gout; Non-Articular Rheumatism; General Pathology; ACTH, Cortisone, and other Steroids; Other General Subjects. At the end of each section is a list of titles of articles noted but not abstracted. Not all sections may be represented in any one issue.

The section "ACTH, Cortisone, and other Steroids" includes abstracts and titles of articles dealing with steroid research which, although not directly concerned with the rheumatic diseases, may make an important contribution to knowledge of the scope and *modus operandi* of steroid therapy.

Acute Rheumatism

Effect of Short-term Administration of Corticotropin in Active Rheumatic Carditis. WILSON, M. G., HELPER, H. N., LUBSCHEZ, R., HAIN, K., and EPSTEIN, N. (1953). *Amer. J. Dis. Child.*, **86**, 131. 7 figs, 9 refs.

The results of administration of corticotrophin (ACTH) for short periods (average 7 days) to 28 patients with active rheumatic carditis are reported from New York Hospital. As judged by the clinical findings and the results of fluoroscopic examination the attack was quickly arrested in 24 cases in which the eosinophil count was maintained below 10 per c.mm. (treatment considered "adequate"). In four of eight cases in which the eosinophil count rose above 10 per c.mm. (treatment considered "inadequate"), there was a recurrence of symptoms after treatment was discontinued. The arrest of the carditis was more prompt and complete when treatment was begun within 10 days of the onset of the attack; when treatment was started later there was no reversal of cardiac enlargement. During the follow-up period three patients had recurrent attacks; this incidence, the authors point out, is no greater than might be expected. In the authors' view these observations indicate that short-term ACTH therapy is followed by arrest and termination of active carditis, and that it favourably alters the natural course of the disease. *B. E. W. Mace.*

Function of the Adrenal Cortex in Rheumatic Fever. WIENER, S. (1953). *Aust. Ann. Med.*, **2**, 103. 18 refs.

As a measure of adrenocortical function the author determined the eosinopenic response in a small series of children aged between 7 and 13 years admitted to the Children's Hospital, Melbourne, suffering "from the major manifestations of rheumatic fever, including chorea". The response was estimated in four groups tested respectively with 10 mg. ACTH intramuscularly, 0·3 mg. adrenaline subcutaneously, and 60 and 30 mg. ephedrine sulphate given by mouth. Except for those receiving the smaller dose of ephedrine sulphate, all patients showed a significant fall in the eosinophil count after 4 hours. Control observations were made on the previous day, and the timing was arranged to obviate normal diurnal variations.

The author concludes that no evidence is given by this method of examination to suggest any hypofunction of the adrenal cortex or interference with the pituitary-adrenocortical relationship in rheumatic fever. The study was made with a view to substantiating "the presumed allergic reactions in rheumatic fever" based on the belief that ACTH and cortisone inhibit the delayed type of allergic reaction. As a secondary observation it was noted that the normal level of circulating eosinophil cells in this group was somewhat higher than the upper limit of normal defined by Discombe (*Lancet*, 1946, **1**, 195).

Harry Coke.

Effect of Cortisone Therapy on the Incidence of Rheumatic Heart Disease. JOHNSON, A. L., and FERENCZ, C. (1953). *New Engl. J. Med.*, **248**, 845. 5 refs.

At the Children's Memorial Hospital, Montreal, the effect of administration of cortisone on the incidence of heart disease was studied in 100 patients with active rheumatic fever, eighty similar patients who had no cortisone serving as controls. The patients in both groups were between 3 and 14 years of age. The majority of the treated group received 200 mg. cortisone for 2 days and 100 to 150 mg. daily for 28 days or longer. The degree of cardiac involvement was assessed from the results of clinical, electrocardiographic, and fluoroscopic examination.

There was no significant difference between the two groups in the incidence of heart disease. The authors state that the lower death rate in the treated group was not statistically significant, but that in view of the dramatic improvement in many severely ill patients it appeared possible that the death rate from acute rheumatic fever was reduced by the drug. *Oswald Savage.*

Use of Sulfonamides and Penicillin to Prevent Recurrence of Rheumatic Fever. A Twelve-Year Study. ROBERTS, E. (1953). *Amer. J. Dis. Child.*, **85**, 643. 3 refs.

Of 638 children admitted to the Children's Heart Hospital, Philadelphia, with rheumatic fever during the

10-year period 1940-50, 467 were subsequently given various forms of sulphonamide prophylaxis for periods ranging from 3 months to 2 years. During the first 3 years of the period treatment was given only between September 1 and June 1 each year, the dosage ranging from 3 to 6 g. daily to maintain a serum level of 4 to 5 mg. per 100 ml. During the next 7 years treatment was given continuously throughout the year, but the dose used was smaller, varying from 0·5 to 1·0 g. daily. All these children were in hospital while the prophylactic treatment was being given. Only two recurrences occurred in children taking sulphonamides, compared with nine recurrences among 44 control subjects during the same period, and 38 recurrences among 154 patients in a 2-year period before the introduction of prophylactic sulphonamide. In 34 additional cases the patient started taking prophylactic sulphonamide but developed toxic manifestations (chiefly rashes, haematological reactions, and albuminuria) which made it necessary to discontinue the drug. The incidence of toxic manifestations was unrelated to the dosage used.

In view of the toxic complications of sulphonamide prophylaxis, penicillin prophylaxis was substituted in 1950, and up to July 1, 1952, 102 children had been treated, each receiving 100,000 units crystalline benzyl penicillin twice daily by mouth in liquid form. None of these children had a recurrence of rheumatic activity, and none had toxic reactions. *R. S. Illingworth.*

Serum Diphenylamine Reaction in Rheumatic Fever. COBURN, A. F., MOORE, L. V., and HANINGER, J. (1953). *Arch. intern. Med.*, **92**, 185. 2 figs, 2 refs.

It has been reported (Niazi and State, *Cancer Res.*, 1948, **8**, 653) that the patient's serum in several disease states contains increased levels of a substance giving a purple colour with diphenylamine. This reaction is measured by the intensity of the colour reaction of serum added to the diphenylamine reagent. At the Rheumatic Fever Research Institute (Northwestern University), Chicago, raised values were obtained with serum from patients in the acute stage of rheumatic fever, while serum from patients who had recently recovered and others who had shown no signs of activity for one year gave normal values. The intensity of this colour reaction and the erythrocyte sedimentation rate showed close parallelism. The substance in the serum reacting with diphenylamine is unknown, but the authors claim that connective tissue is a rich source of the substance, and that its concentration in the blood is related to the intensity of the inflammatory process.

[Yet another empirical test is added to the already existing battery of tests, with no proof of its superiority over any of the older methods of assessment of activity in rheumatic fever.] *G. Loewi.*

Sodium Salicylate in Rheumatic Fever; Effect of Adjuvant Medication. HENDERSON, L. L. (1953). *Amer. J. med. Sci.*, **225**, 480. 20 refs.

Patients with rheumatic fever in a U.S. Army hospital and varying in age from 18 to 38 years were given 1·6 g. enteric-coated sodium salicylate every 4 hours, together with one of the following adjuvant drugs: sodium bicarbonate, magnesium trisilicate, aluminium hydroxide gel, aluminium hydroxide tablets. Blood samples for salicylate determination were taken at 8 a.m. every second day.

In 24 patients receiving enteric-coated sodium salicylate alone, an average plasma salicylate level of 42·2 mg./100 ml. (range 33·4 to 57·0 mg./100 ml.) was found. In a further sixteen patients, the administration of 1·6 g. sodium bicarbonate with their salicylate depressed the plasma salicylate level, the average reading being 29·8 mg./100 ml. (range 24·9 to 37·0 mg.). Several of these patients complained of bloating and gaseous eructations. The average plasma salicylate level in seventeen patients receiving 0·65 g. sodium bicarbonate with each dose of salicylate was 35·9 mg./100 ml. (range 26·7 to 48·6 mg.); there were few complaints of gastric upset. In thirteen patients receiving 1·0 g. magnesium trisilicate with each dose of salicylate, the levels ranged from 38·8 to 54·2 mg./100 ml. (average 43·0 mg.); some patients given the higher concentrations suffered from dyspnoea, nervousness, and anorexia. The figures in nine patients receiving aluminium hydroxide in tablet form were: average 46·5 mg./100 ml.; range 40·0 to 54·0 mg. In this group nervous irritability accompanying the higher salicylate levels was prominent. Of the sixteen patients started on aluminium hydroxide gel, 8 to 16 ml. for each dose of salicylate, five became so nauseated that they could not continue. The average plasma salicylate level of the remaining eleven patients in this group was 49·8 mg./100 ml. (range 42·8 to 59·2 mg.).

Sodium bicarbonate was found to have the effect of restoring toward normal the diminished carbon dioxide combining power resulting from salicylate therapy. Magnesium trisilicate and aluminium hydroxide gel and tablets were as effective as sodium bicarbonate in relieving gastric distress, but did not lower the plasma salicylate level or raise the carbon dioxide combining power. Incidental observations were the apparent lack of effect of salicylate on the elevated erythrocyte sedimentation rate and the prolonged P-R interval, and the absence of any haemorrhagic manifestations. *Norval Taylor.*

Further Experience with Aureomycin in the Treatment of Acute Rheumatism in Children. (Ďalšie skúsenosti s aureomycínovou liebčbou akútneho reumatizmu u detí.) SIKULA, L. (1953). *Lék. Listy*, **8**, 213.

The author reports his results in 35 children with acute rheumatism treated with aureomycin. Of these, 27 were observed for a period of 2 years, and are divided into three groups according to the progress made: (1) four children, three relapsed because treatment was too short, having lasted only 6, 5, and 10 days respectively, and the dosage was too low (0·5, 5, and 6 g.). The fourth patient suffered a recrudescence of the acute rheumatic process, with decompensated mitral stenosis 6 months after cessation of treatment, but became symptomless after a 12-day course of aureomycin (total dose 8 g.).

(2) six patients, treatment was begun in three children, 4, 28, and 14 days after the onset of the attack, and lasted

16, 23, and 15 days, the dosage being 8, 16, and 16 g. In these three all clinical signs disappeared without any other antirheumatic treatment; the electrocardiogram, which had shown a myocardial change in the child in whom treatment had been started only after 28 days, returned to normal after 23 days. In the other three the erythrocyte sedimentation rate became normal after 11, 12, and 7 days of treatment with total doses of 12, 12, and 16 g. All six children were in good health 4 months after cessation of treatment.

(3) Seventeen children, no further attack occurred for 10 to 24 months, in spite of recurrent tonsillitis or infectious disease. Restriction of activities or school attendance was imposed on only two patients with compensated mitral stenosis; tonsillectomy was performed in three children. In seven cases treated 4 to 14 days (average 8) after the onset of the first attack, the cardiac findings were normal; in four patients treated 7 to 21 days (average 11) after the onset, mild cardiac involvement was observed; in six cases in which treatment with aureomycin was delayed up to 12 months after a repeated attack, severe mitral and aortic valvular disease was found. Nevertheless, in all cases the electrocardiogram was within normal limits at the time of follow-up examination.

The gain in weight amounted from 2·1 to 10 kg. (average 4·3), with a rapid weight increase of 7 to 10 kg. during prepuberty and puberty. Dental caries was found in ten cases of the last group. The blood picture was normal in all children, and there was no complaint of joint or muscle pain. The author advises the continuation of treatment with aureomycin for a maximum of 28 days, with full dosage for 21 days. The effective dose seems to be 40 to 50 mg./kg. body weight per day. Vitamin B or nicotinic acid was simultaneously given to all the children, and additional vitamin K to some of them. The degree of residual cardiac damage seemed to depend upon the time lag between the onset of the disease and beginning treatment. Nevertheless, even cases with severe cardiac involvement resistant to other antirheumatic therapy, responded well. The treatment was well tolerated even in younger children. It is stressed, however, that aureomycin treatment cannot replace the therapeutic measures indicated in cases of disturbed circulation. In hyperactive cases with recurrent relapses, repeated small transfusions with blood from women in the 4th to 6th month of pregnancy are advised. *M. Dynski-Klein.*

Treatment of Acute Chorea. (О лечении больных острой хореей) MALKINA, M. G. (1953). *Zh. Nevropat. Psikhiat.*, **53**, 139. 3 figs, 5 refs.

The pathogenesis of chorea has been studied by Russian workers on the basis of Pavlov's theories, the symptoms being attributed to cerebral excitation (and subsequent inhibition) caused by cerebral oedema. Investigations carried out at the Saratov Medical Institute have further shown that this oedema affects especially the subcortical centres and that it is part of a general disturbance of water metabolism.

With the aim of causing dehydration and thus reducing cerebral oedema, two methods of treatment have been used in cases of chorea.

(1) "Combined osmotherapy", consisting of intramuscular injections of 5 to 10 ml. of 25 per cent. magnesium sulphate solution (the dose being diminished with clinical improvement) and repeated lumbar puncture. Of 21 patients so treated, four were cured after 18 days and eleven after 19 days; the remaining six show some degree of improvement.

(2) A course of six to twelve injections of a mercurial diuretic given at 3-day intervals. Of 27 patients treated in this way, thirteen were cured after 19 days and eleven were improved; the condition of two others was unchanged and in one it became worse.

In both groups, 1 to 3 g. of sodium salicylate was given daily in addition. *W. Szaynok.*

Rheumatic "Activity" as judged by the Presence of Aschoff Bodies in Auricular Appendages of Patients with Mitral Stenosis. 1. Anatomic Aspects. DECKER, J. P., HAWN, C. VAN Z., and ROBBINS, S. L. (1953). *Circulation* (*N. Y.*), **8**, 161. 6 figs, 28 refs.

Histological study at the Peter Bent Brigham and Boston City Hospitals of 183 auricular appendages, out of a total of 223 removed at operation from patients thought to be free of active carditis, showed the presence of Aschoff bodies in 83 (45 per cent.), these bodies being numerous (up to 10 or 12) in 21 cases (11·5 per cent.). They were located in the endocardium or, more commonly, in the loose-structured subendocardium; none were in the myocardium proper. Of 172 appendages examined, endocardial thrombosis was present in 71 (41 per cent.), but in these cases the incidence of Aschoff bodies was low. In six of the 22 cases coming to necropsy and showing Aschoff bodies, it was found that when these lesions were frequent in the left auricular appendage, they were also frequent in the left ventricular myocardium and *vice versa*. *A. C. Lendrum.*

Psychological Aspects of Pediatrics. Emotional Aspects of Rheumatic Fever in Children. BRAZELTON, T. B., HOLDER, R., and TALBOT, B. (1953). *J. Pediat.*, **43**, 339. 12 refs.

Pathogenesis of Transitory Disturbances of Conduction in the Heart in Acute Rheumatism. (Rilievi nella patogenesi dei disturbi transitori di eccitoconduzione cardiaca in corso di reumatismo acuto focale.) FRANCESCONI, M., and BOVO, G. (1953). *Folia cardiol.* (*Milano*), **12**, 311. 7 figs, 31 refs.

Prevention and Treatment of Rheumatic Fever. ELGHAMMER, H. W. (1953). *Illinois med. J.*, **104**, 187.

Experience with Gantrisin as a Prophylactic Measure in Rheumatic Fever, with special reference to the Ability of Children to tolerate the Drug over a Prolonged Period. KURTZ, C. M. (1953). *J. Urol.* (*Baltimore*), **70**, 802.

Chronic Articular Rheumatism
(Rheumatoid Arthritis)

Treatment of Rheumatoid Arthritis with *p*-Aminobenzoate and Acetylsalicylic Acid. ZARAFONETIS, C. J. D., STEIGER, W. A., GINSBURG, I. W., and HEATHER, A. J. (1953). *Arch. intern. Med.*, **92**, 204. 1 fig., 11 refs.

This study was made on 44 patients suffering from chronic rheumatoid arthritis of long standing who were showing signs of deterioration. The investigation was conducted by three separate groups of workers in two different cities (Philadelphia and Wilmington, Delaware) and was carried out mainly on out-patients. Quite apart from the two drugs being tested, namely, *p*-aminobenzoic acid and acetylsalicylic acid, some patients received doses of cortisone, "rarely exceeding 25 mg. per day", and three patients were given physiotherapy. Potassium *p*-aminobenzoate was given in six 2-g. doses per day, and 0·6 g. acetylsalicylic acid was given four times a day.

It is claimed that 34 of the patients were improved but that 3 months elapsed from the beginning of treatment until the improvement became apparent. This was characterized by a decrease in joint pain, heat, swelling, and tenderness, and in nodule size, and increased freedom of movement, with loss of fever and gain in weight [but no detailed results are given].

[This report indicates that treatment with a combination of the drugs named may be of some value. However, the manner in which this trial was conducted does not allow definite conclusions to be drawn.]

G. Loewi.

Thiosemicarbazone in Rheumatoid Arthritis. [In English.] VIRKKUNEN, M., and LEHTINEN, L. (1953). *Ann. Med. intern. Fenn.*, **42**, 249. 1 fig., 14 refs.

The literature on the use of thiacetazone ("thiosemicarbazone") in the treatment of tuberculosis and rheumatoid arthritis is reviewed. Heilmeyer found that administration of thiacetazone in rheumatoid arthritis was followed by a rapid fall in the erythrocyte sedimentation rate (E.S.R.), with a remission in joint symptoms. He suggested that the drug had a cortisone-like effect which it exerted by blocking mineral corticoids and increasing the action of glycocorticoids. The object of the present investigation, which was carried out at the Kivelä Hospital, Helsinki, was twofold:

(1) to determine the effect of thiacetazone in rheumatoid arthritis;

(2) to determine whether this drug acted synergistically with cortisone—for example, by exerting a toxic effect on the liver and delaying cortisone metabolism.

A daily dose of 0·2 to 0·3 g. thiacetazone was given for an average of 80 days to 37 patients suffering from rheumatoid arthritis, four of them receiving both thiacetazone and cortisone. Although considerable improvement was observed, in 26 of the 37 this was transient, relapse following when administration of the drug ceased. The E.S.R. fell markedly in most of the patients but rose again when treatment was discontinued. Toxic reactions, noted in 25 patients, consisted in nausea and vomiting, skin rash, granulocytopenia, albuminuria, and urobilinuria; in five cases treatment had to be stopped because of severe nausea. It was found that toxic reactions were closely related to the size of the dose, none being observed when the dose of thiacetazone was less than 0·2 g. daily. No evidence of a synergistic action was found in the four patients who received both thiacetazone and cortisone.

The authors conclude that the transient effect of thiacetazone and the serious toxic reactions render this drug of little value in the treatment of rheumatoid arthritis. [There was no control investigation.]

W. Tegner.

Treatment of Rheumatoid Arthritis with Aurothioglycanide (Lauron). BATTERMAN, R. C. (1953). *J. Amer. med. Ass.*, **152**, 1013. 4 refs.

It is pointed out that the results of prolonged treatment of rheumatoid arthritis with cortisone and ACTH leave much to be desired. Though there is good functional improvement the degree of improvement in terms of rheumatoid activity is usually Grade 2 (major) or Grade 3 (minor), rarely Grade 1 (complete remission).

The author, from New York Medical College, describes his experiences with a gold preparation, aurothioglycanide ("Lauron"), in the treatment of 69 patients over a period of 8 years. If the disease was recent in onset and not very active, 25 mg. was given; this dose was always given initially if the patient had had toxic effects from gold therapy previously. The majority of patients received 50 mg. initially, this initial dose being given once a week for 3 weeks. If no improvement or toxic effects occurred the dose was then doubled, and again increased, if necessary, at 8 or 10 weeks; it never exceeded 150 mg. weekly. This dosage level was continued until improvement was well established, but if after 6 months there was no improvement, treatment was discontinued. In one group of patients who improved, treatment was discontinued, while in another, a maintenance dose of 50 to 150 mg. at 2- or 4-weekly intervals was given. The total duration of therapy varied between 5 weeks and 3 years.

Altogether 26 patients, regardless of the stage of the disease, showed improvement with the initial phase of treatment. When patients with early arthritis (Stage 1 or Stage 2) were considered, it was found that in just over one-half there was complete remission or major improvement. This initial response was further enhanced by maintenance therapy, since in fifteen out of seventeen there was a satisfactory end-result.

A comparison of the incidence of toxic effects and their severity with those observed in a series of patients receiving aurothioglucose in another clinic suggested that aurothioglycanide was less toxic. *C. E. Quin.*

Urinary Steroid Excretion in Rheumatoid Arthritis. Changes in Ketonic and non-Ketonic Fractions during Hormone Therapy. KELLIE, A. E., and WADE, A. P. (1953). *Brit. med. J.*, **2**, 594. 6 figs, 12 refs.

In continuation of the study reported by Copeman and others (*Brit. med. J.*, 1952, **1**, 397), the authors now give further details of 17-ketosteroid excretion after

cortisone administration, and also report changes after ACTH therapy. A new method of analysing the non-ketonic fraction has revealed changes not previously reported. The work was carried out at the Middlesex Hospital Medical School, London. Urine was collected from normal male and female subjects, and from patients with rheumatoid arthritis before and during treatment with ACTH and cortisone. The benzene extract of the urine hydrolysate was fractionated by the usual methods and final fractions (ketonic alcohols, ketonic non-alcohols, non-ketonic 3α-alcohols and non-ketonic 3β-alcohols) were analysed chromatographically. The non-ketonic fractions were assayed by conversion of the alcohols to 3 : 5-dinitrobenzoates (Kellie and others, *Biochem. J.*, 1953, **53**, 578).

Comparison of the steroid excretion in the normal subjects and in untreated arthritic patients showed that:

(1) the aetiocholanolone : androsterone ratio is higher in the latter, a change already reported in at least one other pathological condition;

(2) the ketonic non-alcohols are unchanged;

(3) the non-ketonic 3α-alcohols (probably mono-, di, and tri-hydroxy alcohols) are considerably reduced in quantity;

(4) the amount of non-ketonic 3β-alcohols excreted in both normal and rheumatoid arthritic subjects was negligible.

A close study was made of three arthritic patients who were receiving hormone therapy: ACTH, cortisone, and ACTH followed by cortisone. The administration of ACTH led to a great increase in steroid excretion, which was reflected in all fractions but was mainly due to increased output of androsterone and acetocholanolone. Treatment with cortisone was followed by an irregular small rise in 17-ketosteroids excretion, mainly in the ketonic alcohols and particularly aetiocholanolone; it is pointed out that this finding is contrary to that of other workers. *Nancy Gough.*

Investigation of Combined Treatment with ACTH and *para*-Aminobenzoic Acid in Rheumatoid Arthritis. [In English.] DALGAARD, O. Z. (1953). *Acta endocr.* (*Kbh.*), **13**, 39. 10 figs, 16 refs.

In view of various reports of the favourable effect of using *para*-aminobenzoic acid (PABA) as an adjuvant to cortisone in the treatment of rheumatoid arthritis, the author set out to determine whether a combination of PABA and ACTH (corticotrophin) had a similar synergistic or additive effect, and whether PABA alone influenced hormone production by the adrenal cortex. Accordingly, five patients suffering from rheumatoid arthritis of long standing were treated at the Kommune-hospitalet, Copenhagen, with PABA and small doses of ACTH. They were first given 10 mg. ACTH and 12 g. PABA daily for 5 days; then, after a 5-day interval, they received 10 mg. ACTH daily for 5 days without PABA, and finally, after a further 5-day interval, the first course was repeated. The effect of treatment was assessed from clinical appearances and by determination of the eosinophil count and urinary 17-ketosteroid excretion.

The administration of these small doses of ACTH produced some slow symptomatic improvement in four of the five patients treated, with a rise in 17-ketosteroid excretion and a fall in eosinophil count, during the treatment periods, but the addition of PABA appeared to make no difference to the response.

A second group of five patients suffering from other diseases were given 12 g. PABA daily for 5 days, the urinary 17-ketosteroid excretion being determined daily. The drug had no demonstrable effect. *G. Loewi.*

Treatment of Rheumatoid Arthritis with Hypoglycaemia. (Hypoglykæmibehandling af polyarthroitis chron. prim.) RIISING, P. V., and HOLST, J. E. (1953). *Ugeskr. Læg.*, **115**, 558. 6 refs.

At Roskilde County and Municipal Hospital, Denmark, fifteen cases of rheumatoid arthritis were treated by the induction of hypoglycaemia with insulin. Each morning for 4 weeks the fasting patient was given sufficient insulin to produce hypoglycaemic symptoms, a carbohydrate meal being given at the end of 3 hours unless the severity of the symptoms necessitated administration of glucose at an earlier stage. The status of patients was assessed on appearance and performance of joints and on the erythrocyte sedimentation rate before, during, and after the course of treatment. A great improvement was noted in four cases, slight improvement in six, and no improvement in five immediately after the course. At a follow-up examination 4 to 9 months later, however, there was great improvement in one case, slight improvement in four, and none in ten. *B. Nordin.*

Ascorbic Acid, Glucose-1-Phosphate, and Lysergic-Acid Diethylamide in Rheumatoid Arthritis. LOVELL, R. R. H., OSBORNE, J. A., GOODMAN, H. C., and HUDSON, B. (1953). *Lancet*, **1**, 970. 1 fig., 10 refs.

The authors recall that Long and others (*Lancet*, 1951, **1**, 1085) postulated that, on the analogy of the diminution of experimental tuberculin hypersensitivity in guinea-pigs by cortisone and ACTH, other factors influencing such sensitivity might also influence arthritis in man. They also suggested that the action of ACTH and cortisone is mediated through ascorbic acid, and the effect of this substance was therefore tried in patients with arthritis, as were the effects of glucose-1-phosphate and lysergic acid diethylamide, both of which modify experimental tuberculin sensitivity.

For the tests carried out at St. Mary's Hospital, London, ten patients with rheumatoid arthritis and one with polyarteritis nodosa with predominant involvement of the joints were chosen. They were kept on a scorbutic diet and all were given acetylsalicylic acid, 30 to 60 gr. (2 to 4 g.) daily, and codeine when required. In one patient, the scorbutogenic diet improved the arthritis, but this improvement continued when ascorbic acid was administered, and cortisone and ACTH produced further improvement while the patient was still on this diet. Two other patients experienced no change in their symptoms, while tuberculin sensitivity increased in one patient, but decreased when ACTH was given. In four patients receiving glucose-1-phosphate and in a further

four given lysergic acid diethylamide, no effect on the arthritis or tuberculin sensitivity could be detected.

It is clear that no evidence was found to support an analogy between experimental tuberculin sensitivity and the tissue reactions in rheumatoid arthritis. The possibility is suggested that the tuberculin reaction in the guinea-pig and in man may differ. *G. Loewi.*

Effect of β-Tetrahydronaphthylamine in Rheumatoid Arthritis. (Über die Wirkung von β-Tetrahydronaphthylamin bei primär-chronischer Polyarthritis.) LÜDERITZ, B., and MEYER, K. A. (1953). *Klin. Wschr.*, **31**, 492. 2 figs, 26 refs.

β-Tetrahydronaphthylamin is primarily a sympathetic stimulant with some action on the parasympathetic system. During an investigation of its action on the vegetative nervous system, carried out in the Medical Clinic of the University of Münster, it was noticed that individuals suffering from rheumatoid arthritis were able to move the affected joints more easily and with less pain after being given the drug. The possible analgesic properties of the drug were then tested by determining its effect on the strength of electric stimulus necessary to elicit pain when applied to the region of the median nerve at the wrist. The experiment showed that the drug had no effect on sensitivity to pain in rheumatic and non-rheumatic subjects alike. Another possible mode of action was suggested by the observation that muscle tone appeared to be decreased after administration of the drug, non-rheumatic subjects complaining that their limbs felt heavy and useless, although movements could be carried out with an effort. Patients with rheumatoid arthritis, on the other hand, were very impressed by their increased activity and lack of pain. As a working hypothesis, therefore, it was assumed that the drug caused muscular relaxation and a loosening of the capsules of affected joints, relief of pain following automatically. No effect of the drug on the electrical reactions of muscles could be demonstrated electromyographically, but investigation of its effect on intramuscular tension by the technique of Henderson (involving measurement of the resistance to intramuscular injection of saline) in eighteen patients with rheumatoid arthritis showed that a definite reduction of tension occurred on injection of β-tetrahydronaphthylamine in all fifteen cases in which the drug also relieved joint pain. In one case a fall of tension was unaccompanied by relief of pain, but this was attributed to bony ankylosis; in the remaining two cases there was no fall in tension and no relief of pain.

It is not suggested that the drug should be used as a therapeutic agent in its own right. There is, in fact, evidence that the initially effective dose of 0·025 g. has to be doubled after 7 days. Its main value would appear to be in facilitating active and passive movement of the affected joints, particularly when supplies of cortisone are not available. In 28 cases (22 women, 6 men) of rheumatoid arthritis the drug was given half an hour before physiotherapy (in 20 cases subcutaneously and in 8 by mouth). The results were "excellent" in fifteen and "good" in eleven; no toxic effects were observed. *D. Preiskel.*

Treatment of Rheumatoid Arthritis with Atebrin. [In English.] OKA, M. J. (1953). *Ann. med. intern. Fenn.*, **42**, 215. 5 refs.

The author briefly reviews the literature dealing with "Atebrin" (mepacrine), and recalls the claim made by Freedman and Bach that the drug may be of value in the treatment of rheumatoid arthritis. In the series here reported, seventeen female and seven male patients suffering from active rheumatoid arthritis were treated with 0·1 g. Atebrin three times daily for one week and then with 0·1 g. twice a day as a maintenance dose. In two of these patients the activity of the rheumatoid arthritis ceased completely after 8 weeks' treatment. In all the other patients signs of activity remained after periods of treatment of up to 12 weeks, but seven were subjectively improved, and eleven showed slight improvement. There were no serious toxic reactions, but yellowing of the skin usually appeared in the second week of treatment. Four detailed case histories are given.

The author concludes that Atebrin has some antirheumatic action, but that this action is sufficiently efficacious in only about one-third of the patients treated. The series reported was uncontrolled. *W. Tegner.*

Splenectomy in Rheumatoid Arthritis. STEINBERG, C. LER. (1953). *Ann. intern. Med.*, **38**, 787. 15 figs, bibliography.

It has been shown, both experimentally in animals and in the human subject, that hypophysectomy results in atrophy of the spleen and, conversely, that splenectomy leads to hypertrophy of the anterior pituitary gland. The author of this paper considers Felty's syndrome to be a variant of rheumatoid arthritis, and has observed a hyperplastic marrow associated with agranulocytopenia or leucopenia in affected cases. He presents detailed reports of three cases of Felty's syndrome in which splenectomy was performed at the Rochester General Hospital, New York. In two of these there was marked improvement, not only in the blood picture but also in the arthritic condition, following operation. In the third case similar improvement followed splenectomy, but leukaemia developed 3 years later. Short reports are also given of three further patients who developed Felty's syndrome but had been treated with cortisone or corticotrophin. In one case, although both the splenomegaly and the leucopenia disappeared during cortisone treatment, they returned 4 weeks after its cessation. In the remaining two cases, splenomegaly developed after cortisone and corticotrophin therapy respectively. In these cases treatment with the hormones led to a temporary improvement in the blood picture and a diminution in size of the spleen, but did not prevent the development of splenomegaly or result in permanent reversal of splenomegaly if already present.

Splenectomy appears to be the treatment of choice in cases of Felty's syndrome, and it is suggested that one effect of removal of the spleen may be to bring about hypertrophy of the anterior lobe of the pituitary and thus increase the natural supply of corticotrophin.

R. E. Tunbridge.

Some Observations on Anaemia in Rheumatoid Arthritis. JEFFREY, M. R. (1953). *Blood*, **8**, 502. 36 refs.

The nature of the anaemia in rheumatoid arthritis was studied at the Royal National Hospital for Rheumatic Diseases, Bath, in a varying number of active cases of the disease, with special regard to changes in the peripheral blood and bone marrow, blood, plasma, and corpuscle volumes, and alterations in iron metabolism. Estimations of blood values were made on one hundred cases or more, and the anaemia was found to be predominantly normochromic or hypochromic in type, the reduction in haemoglobin value and erythrocyte count being greater in the more active cases. Blood values bore no relationship to the duration of the disease or the age of the patient, and did not reveal any haemodilution.

A study of reticulocytes, faecal urobilinogen, and plasma bilirubin on fourteen, nineteen, and twelve cases respectively revealed no significant abnormality, except in one case in which these values were raised. Sternal marrow smears showed no major abnormality, but there was a slight tendency to hypercellularity, arrest of maturation, and delayed haemoglobination of the normoblasts. The iron-binding capacity of the plasma was in most cases within normal limits, but estimation of the serum iron level and intestinal iron-absorption capacity revealed evidence of defective iron assimilation. A small proportion of cases which were refractory to iron given by mouth showed improvement of the anaemia when iron was given intravenously, but the response was not always complete. *Mary D. Smith.*

Still's Disease treated with ACTH and Cortisone. WELCH, R. G., and FORSYTH, C. C. (1953). *Gt. Ormond Str. J.*, **5**, 1. 3 figs, 9 refs.

The results of administration of cortisone and ACTH in fifteen cases of Still's disease are reported. In spite of a high dosage and a long period of treatment side-effects were fewer than expected. The typical moon-face was common, but there was no electrolyte disturbance or significant glycosuria. Of the fifteen patients three died and two were lost to subsequent follow-up. The condition was well controlled by cortisone in one patient and partially controlled in two. One other patient had limitation of movement, although the disease was quiescent, and six were well at the time of reporting.

The authors conclude that administration of ACTH or cortisone modifies the signs and symptoms of Still's disease more consistently than any other form of treatment, and that while the outcome in this series is not significantly better than that observed by other workers before these drugs were available, it may prove to be better in time. *Oswald Savage.*

Genetics of Rheumatoid Arthritis. Analysis of 224 Families. STECHER, R. M., HERSH, A. H., SOLOMON, W. M., and WOLPAW, R. (1953). *Amer. J. hum. Genet.*, **5**, 118. 1 fig., 23 refs.

The authors made detailed inquiries into the family history in 224 cases of rheumatoid arthritis collected from private practice and a number of clinics and hospitals in Cleveland, Ohio. Similar inquiries were made in a control series of 488 patients, all free from rheumatoid arthritis, although 122 had Heberden's nodes, 59 ankylosing spondylitis, and 47 gout.

The incidence of rheumatoid arthritis among 1,443 relatives of affected individuals was 3·4 per cent. [figures corrected by abstracter] that among male relatives being 1·9 per cent., and among females 4·6 per cent.; of the 775 relatives who were over 50 years of age, 5 per cent. were affected. Of 2,759 relatives of patients in the control group, 0·58 per cent. were affected (males 0·52 per cent., females 0·64 per cent.), the incidence among the 1,530 who were over 50 being 1·1 per cent. Lack of agreement between the observed numbers of sibships having 0, 1, 2, 3, and 4 cases of the disease, and those expected on the basis of the Poisson distribution provides further evidence of a familial tendency. While the ratio of females to males among all affected relatives was approximately 2·5 to 1, any question of transmission of susceptibility to the disease as a sex-linked factor was ruled out by examination of pedigrees. There was found to be no association between parity and susceptibility.

After correcting for small family size and for age, the data are consistent with transmission as an autosomal dominant gene with approximately 50 per cent. penetrance or as an autosomal recessive gene with about 70 per cent. penetrance, but the latter hypothesis was ruled out in the extensive pedigree (including ten cousin marriages) reported by Whittinghill and Hendricks (*J. Elisha Mitchell Sci. Soc.*, 1951, **67**, 185). From estimates of the incidence of rheumatoid arthritis in the population of the whole area concerned, the gene frequency as a dominant with 50 per cent. penetrance would be 0·006, and as a recessive with 70 per cent. penetrance, 0·091.

The authors discuss the variations in penetrance and excessive irregularities of expressivity of the hereditary factor in rheumatoid arthritis in relation to the various internal and external ancillary aetiological factors involved. *R. H. Cawley.*

Rehabilitation of the Hand in Rheumatoid Arthritis. BAKER, F. (1953). *Arch. phys. Med.*, **34**, 299. 4 figs, 3 refs.

The author prefaces this paper with a detailed description of the anatomy and function of the normal hand, special reference being made to the metacarpophalangeal joint. The sequence in the development of deformities as a result of rheumatoid arthritis is then described, the main deformities being subluxation and flexion of the metacarpophalangeal joint due to a loose capsule, and ulnar deviation due to gravity and unequal muscle forces.

A programme of exercises to be given by the physiotherapist is outlined, the aim of the exercises being correction of the alignment of the phalanx on the metacarpal, followed by extension of the metacarpophalangeal joint, and finally by extension of the phalangeal joints. In closing the hand, flexion of the phalangeal joints should be carried out first and then flexion of the metacarpophalangeal joint. *J. B. Millard.*

Agglutination of Sensitized Sheep Erythrocytes by Cold Precipitable Serum Substances in Rheumatoid Arthritis. [In English.] SVARTZ, N., and SCHLOSSMANN, K. (1953). *Acta med. scand.*, **146**, 313. 2 refs.

Liver Function in Rheumatoid Arthritis. (Beitrag zur Leberfunktion bei der primär chronischen Polyarthritis.) SCHMID, J. (1953). *Med. Klin.*, **48**, 1322. 34 refs.

Tissue Analysis with Radioactive Phosphorus in Rheumatoid Arthritis. (Gewebsanalysen mit radioaktivem Phosphor bei chronischer Polyarthritis.) LÖVGREN, O., and ÖRSTRÖM, A. (1953). *Z. Rheumaforsch.*, **12**, 257. 9 refs.

Cardiac Lesions in Rheumatoid Arthritis. STEELE, C. W. (1953). *J. Maine med. Ass.*, **44**, 308. 3 figs, 2 refs.

Anthropological Observations on Patients with Rheumatoid Arthritis. (Anthropologische Beobachtungen bei primärchronischen Arthritikern.) PLÜGGE-HEIDELBERG, H. (1953). *Z. Rheumaforsch.*, **12**, 231.

Rheumatoid Arthritis in Industrial Medicine. WATKINS, A. L. (1953). *N.Y. St. J. Med.*, **53**, 2330. 2 refs.

Combined Treatment of Rheumatoid Arthritis with Cortisone and "Butazolidin" [Phenylbutazone]. (Kombinationstherapie bei chronischer Polyarthritis mit Cortison und Butazolidin.) GSELL, O., and RECHENBERG, H. K. VON (1953). *Schweiz. med. Wschr.*, **83**, 1079. 2 figs, 20 refs.

Artisone Therapy in Rheumatoid Arthritis. LEFKOVITS, A. M. (1953). *Rheumatism*, **9**, 70. 5 figs, 15 refs.

Diagnostic and Prognostic Test for Rheumatoid Arthritis. (Odczyn rozpoznawczo-rokowniczy w przewleklym gośćcu stawowym.) STAWECKI, J. (1953). *Pol. Tyg. lek.*, **8**, 1553.

Electromyographic Diagnostic Methods in Rheumatoid Arthritis. NEWMAN, M. K., GOLDSTEIN, A. S., and WALL, P. (1953). *J. Mich. med. Soc.*, **52**, 956 and 985. 3 figs, 13 refs.

Ocular Manifestations of Still's Disease. (Les manifestations oculaires de la maladie de Still.) BONNET, P., and BONNET, I. (1953). *Bull. Soc. Ophtal. Franç.*, 379.

Band-shaped keratitis, plastic iritis and cataract are the most common ocular manifestations of this affection which is similar to chronic polyarthritis. *J. Rougier.*

(Osteo-Arthritis)

Late Results of Treatment of Congenital Dislocation of the Hip. MULLER, G. M., and SEDDON, H. J. (1953). *J. Bone Jt Surg.*, **35B**, 342. 4 figs, 10 refs.

This is a detailed statistical analysis of 264 cases of congenital dislocation of the hip treated at the Royal National Orthopaedic Hospital, London, in the period 1891-1940. The cases analysed are those in which the patient was traced and examined during the years 1949-50, and are regarded as presenting a more favourable picture than would probably be found in the whole series of 889 cases treated during the 50-year period. [The report does not easily lend itself to condensation and the reader is recommended to study the original. Some of the conclusions drawn by the authors are summarized below.]

The results of closed reduction gave "reason for sober satisfaction", being satisfactory in four-fifths of the unilateral cases and in two-thirds of the bilateral cases if treatment was instituted before the age of 3 years. Immediate open reduction gave only moderate results in the nine cases studied. Of secondary operative procedures, the shelf operation was the most successful, giving encouraging results in two-thirds of the cases. In general, the outcome of open reduction was bad, the results being satisfactory in only four out of twenty cases. Rotation osteotomy "presented a dismal picture", having been effective in only four out of nine cases. The effective life of the successfully treated hip appears to be between 25 and 30 years, after which the joint becomes troublesome in about 50 per cent. of cases. *John Charnley.*

Hip Derangements seen in Cerebral Palsied Children. MATHEWS, S. S., JONES, M. H., and SPERLING, S. C. (1953). *Amer. J. phys. Med.*, **32**, 213. 7 figs, 4 refs.

The authors record and discuss cases of hip-joint deformity observed during routine examinations at the Cerebral Palsy Clinic of the Children's Hospital, Los Angeles, between 1947 and 1952. Among 1,243 patients, ranging in age from infancy up to 19 years, 162 with clinical signs suggestive of hip-joint derangement were noted, and radiographic evidence of abnormality was found in 32 (2·6 per cent.). The deformity was congenital in type in six and non-congenital in 26 (eight with dislocation and eighteen with subluxation or migration of the femoral head). Cases of the latter type were characterized by a valgus position of the femoral head and neck with relation to the shaft, the angle being 150 degrees or more in 23 cases, tear-drop deformity of the head in fifteen cases, and normal acetabulum in all. The majority of the patients suffered from severe spastic quadriplegia, and fifteen of them had never stood or walked to any appreciable extent. Sex distribution was equal, and half were under 5 years of age. Typically, the flexor, adductor, and internal rotator muscles of the hip were stronger, tighter, and more spastic or rigid than those of the opposing groups.

In the majority of cases operative treatment would have had little hope of success either on account of the severity of the condition or the low intelligence of the patient. In six cases of the non-congenital group with migration of the femoral head, however, tenotomy of the adductor longus muscle and neurectomy of the anterior branch of the obturator nerve were performed, followed by straight traction in wide abduction, and resulted after 4 months in a satisfactory position of the femoral head, improvement in walking or standing, and facilitation of nursing care. The authors recommend periodic *x*-ray examination of the pelvis in all cases of cerebral palsy, and are of the opinion that whenever a

valgus of the femoral neck of more than 150 degrees is present, early dislocation of the hip joint may be expected.

V. Reade.

Normal Vascular Anatomy of the Femoral Head in Adult Man. TRUETA, J., and HARRISON, M. H. M. (1953). *J. Bone Jt Surg.*, **35B**, 442. 31 figs, 34 refs.

In an investigation at the Nuffield Orthopaedic Centre, Oxford, of the blood supply to the femoral head in 36 adult specimens obtained post mortem, injections of barium sulphate suspension, silver iodide solution, Berlin blue, and "neoprene latex" solution were made into the medial circumflex femoral artery, the common femoral artery, or the common iliac artery. The barium-sulphate and silver-iodide methods permitted radiological examination of the specimen, either complete, or after sections had been made. Latex casts of the vascular tree, obtained by digestion of the bone and marrow with acid, were dissected under water.

It was found that the vascular patterns established during growth and delineated by the cartilaginous epiphysial plate persist throughout adult life, and the vessels entering the head may thus be termed metaphysial or epiphysial, after the origin of the area which they supply. From the medial circumflex femoral artery arise superior and inferior metaphysial and lateral epiphysial vessels, and from the acetabular branch of the obturator artery a branch passes along the ligamentum teres to form the medial epiphysial artery. The lateral epiphysial vessels, two to six in number, enter the femoral head posteriorly in a thick fibrous sheath, passing transversely above the epiphysial scar to supply most of the head of the bone. The medial epiphysial artery enters the pit on the head of the femur, supplies a small area of surrounding bone, and anastomoses with the lateral epiphysial system. The final distribution of the epiphysial vessels is through a series of radially-arranged vessels which unite to form arcades as they pass towards the articular cartilage. On the upper aspect of the femoral neck, two, three, or four superior metaphysial arteries enter the bone. These pass at first vertically downwards, and then return medially towards the epiphysial scar. The inferior metaphysial arteries enter the under surface of the neck close to the articular cartilage. The metaphysial and epiphysial circulations anastomose across the epiphysial scar, the anastomotic vessels often showing a spiral formation.

These investigations do not demonstrate any diminution in the blood supply to the femoral head with advancing age. The situation of the main epiphysial arteries laterally may explain why these vessels are more liable to injury in adduction than in abduction fractures of the femoral neck and the higher incidence in the former of avascular necrosis of the head of the femur.

Peter Ring.

Treatment of Osteo-Arthritis with "Butazolidin" [Phenylbutazone]. (Die Behandlung der Arthrosis deformans mit Butazolidin.) NATTERER, G., and SCHAAL, K. (1953). *Dtsch. med. Wschr.*, **78**, 1100. 1 fig., 34 refs.

The authors have treated eighty cases of chronic joint disease, of which 68 were cases of osteo-arthritis (mainly of the knees) with phenylbutazone ("Butazolidin"). The drug was injected intramuscularly in doses of 1 g. in a 20 per cent. solution to which a local analgesic had been added, and there were few local or general reactions. The effect was apparent in some cases within 30 minutes, though usually 12 to 24 hours were required. In twelve cases the effect lasted 1 to 3 days, in 48 cases 1 to 2 weeks, and in sixteen cases 4 weeks or longer. The average number of injections was two or three. Improvement, both objective and subjective, was noted, the greatest benefit being obtained in arthritis of the knees and the least when the spine was affected. Of the eighty patients treated, 24 derived prolonged benefit, and 52 substantial relief; four were unaffected.

(In an addendum it is stated that the number of cases treated has subsequently risen to 220, the results obtained being similar to those in the smaller group.)

D. Preiskel.

Treatment of Osteo-Arthritis with Hydrocortisone. (Behandling af osteoarthrosis med hydrocortone.) ANDERSSON, E., and PETERSEN, K. BIRKUM (1953). *Ugeskr. Laeg.*, **115**, 1767. 1 fig., 3 refs.

Osteo-Arthritis treated with ACTH. DALE, M., and AMIL, M. (1953). *J. Mich. med. Soc.*, **52**, 963. 8 refs.

Osteo-Arthritis of the Knee. Importance of Quadriceps Femoris in Mechanism and Management. FRY, R. J., and HOUSE, F. B. (1953). *J. Mich. med. Soc.*, **52**, 967. 9 refs.

(Spondylitis)

Management of Marie-Strümpell Spondylitis with special reference to Long-Term Cortisone Therapy. BAGNALL, A. W., TRAYNOR, J. A., and MCINTOSH, H. W. (1953). *Canad. med. Ass. J.*, **68**, 587. 2 figs, 1 ref.

This article describes the treatment with cortisone of eleven cases of spondylitis, disabled, but considered to be capable of improvement to full wage-earning capacity. These 11 cases, who had previously been under observation and treatment by other methods, without restoration of wage-earning capacity, were treated with an initial course of cortisone, designed to bring about maximal symptomatic remission, and then stopped; further "booster" courses of 5 to 10 days' duration were given as thought necessary, the main indication being increasing functional impairment. The dose was usually 100 mg. per day, either orally or by intramuscular injection.

On the criterion of work capacity, four of these patients showed marked improvement and four others moderate improvement. After 24-30 months on this regime, ten of the eleven patients were in employment on a full-time basis.

The only side-effects encountered were reactivation of controlled epilepsy, during the initial course, in one patient, and gastro-intestinal haemorrhage in two others (which the authors do not ascribe to the cortisone therapy). They consider that this form of treatment has

produced good results, and that it has advantages over the continuous administration of cortisone.

B. E. W. Mace.

Spondylosis Hyperostotica. (Über die Spondylosis hyperostotica.) OTT, V. R. (1953). *Schweiz. med. Wschr.*, **83**, 790. 13 figs, 28 refs.

The author reports on fifteen patients, eleven men and four women, ranging in age from 44 to 78, who complained of pain in the cervico-dorsal spine of varied duration. Radiography showed typical calcification of the anterior longitudinal spinal ligament, giving an appearance which has been likened to that of sugar-icing. These changes were best seen in the cervical and mid-dorsal spine; they are not to be confused with those occurring in spondylitis ankylopoietica or chronic fluorine poisoning.

In contrast to Forestier and Rotés-Querol, who in 1950 described a similar condition under the name of "hyperostose ankylosante sénile" and believed it to be confined to males, the author is able to include four females in his series. He rightly points out that this spondylosis of middle and old age is the condition first described by von Bechterew, while the priority for describing ankylosing spondylitis belongs to Strümpell and Marie. A further point of difference between the two conditions lies in the pathogenesis. Ankylosing spondylitis is to be reckoned among the inflammatory diseases, this word being used in its widest sense, while the disease described in this paper belongs to the degenerative arthroses.

L. Michaelis.

(Miscellaneous)

Natural History of Lupus Erythematosus and its Modification by Cortisone and Corticotrophin (ACTH). COHEN, H., and CADMAN, E. F. B. (1953). *Lancet*, **2**, 305. 4 figs, bibliography.

In this paper from the University of Liverpool the natural history of lupus erythematosus is discussed and the close relationship between the chronic discoid and acute systemic forms of the disease is demonstrated by reference to sixteen cases.

The typical chronic discoid rash was observed in nine cases of lupus erythematosus. On pathological examination no evidence of an increase in the erythrocyte sedimentation rate (E.S.R.) was found and tests for the presence of "L.E." cells were negative. Minor abnormalities included leucopenia and an increase in the serum globulin level. In a further group of seven cases major systemic reactions were observed. One patient, a woman aged 47 years, suffered from chronic discoid lupus erythematosus for 2 years before systemic changes, such as arthritis, pleural effusion, and loss of weight, were noted. After these symptoms had subsided "L.E." cells were still present in the blood. In the remaining six cases in this group the systemic manifestations were increasingly severe. The authors believe that the evidence presented by these cases favours a unitary conception of the disease—for example, the typical chronic discoid rash developed in a woman, aged 40 years, with rheumatoid arthritis, hepatosplenomegaly, pyrexia, leucopenia, and a raised E.S.R.

The response to administration of cortisone or ACTH was minimum in patients suffering from the chronic discoid form of the disease; on the other hand, there was a dramatic improvement in response to these drugs in four patients with systemic lupus erythematosus. Cortisone was given by mouth in a dose of 25 mg. four times daily and ACTH by intramuscular injection in a dose of 25 mg. every 6 hours. All except one of the patients were finally maintained on a daily dose of cortisone which ranged from 37·5 to 75 mg. daily, the exception being a patient who received a maintenance dose of 10 international units ACTH gel at intervals of one week. Although permanent remission was not obtained, the authors believe that the hormone therapy was justified in the cases of acute systemic disease. This treatment should not, however, be given to patients with a mild form of the disease, for spontaneous remissions are obtained less readily in such cases; moreover, hormone therapy may precipitate a systemic spread in patients with chronic discoid lesions.

A. Garland.

Natural History of Lupus Erythematosus Disseminatus. JESSAR, R. A., LAMONT-HAVERS, R. W., and RAGAN, C. (1953). *Ann. intern. Med.*, **38**, 717. 1 fig., bibl.

The introduction of cortisone and corticotrophin in the treatment of lupus erythematosus has emphasized the lack of real knowledge of the natural history of this disease. The authors have reviewed 44 cases of the disorder seen at the Columbia-Presbyterian Medical Center, New York, in the past 15 years, together with 279 reports published in the literature during the period 1948-52. The diagnosis of lupus erythematosus disseminatus in the authors' own cases was based on the ten criteria laid down by Brenner and others (*Amer. J. med.*, 1948, **5**, 288); only those cases were selected from the literature in which at least seven of these diagnostic criteria were fulfilled.

Information as to presenting symptoms was available only in the authors' cases, arthralgia being observed in 48 per cent., fever in 25 per cent., malaise in 18 per cent., loss of weight in 14 per cent., skin lesions in 14 per cent., and Raynaud's phenomenon in 11 per cent. Fever was present at some time during the illness in nearly all the cases reviewed. Rashes were observed in 69 per cent. of the authors' cases and in 84 per cent. of those culled from the literature; arthritis or arthralgia in 76 and 77 per cent. respectively; and cardiac manifestations in 70 and 68 per cent. respectively. Comparative information relating to other symptoms and signs and to laboratory and necropsy findings is given. Of the authors' patients 13 (30 per cent.) were alive after 5 years. In the reports from the literature it was much more difficult to determine the time of onset of symptoms, but in 22 per cent. of cases in which assessment was possible, the patient was alive after 5 years.

R. E. Tunbridge.

The "Pararheumatic" Arthropathies. FRIEDMAN, H. H., SCHWARTZ, S., TRUBEK, M., and STEINBROCKER, O. (1953). *Ann. intern. Med.*, **38**, 732. 8 figs, 35 refs.

The authors define the pararheumatic arthropathies as the musculo-articular manifestations occurring in the

"pararheumatic" diseases—acute disseminated lupus erythematosus, polyarteritis nodosa, diffuse scleroderma, and dermatomyositis. After a full discussion of the relevant literature the authors review 36 cases of pararheumatic arthropathy admitted to the Bellevue Hospital, New York, from 1938 to 1947, describing eight of them in detail. They stress the high incidence of arthropathy in the pararheumatic diseases and its frequency as a presenting symptom, and in their opinion a pararheumatic disorder should be considered if a case of so-called fibrositis is associated with fever; also in acute or subacute polyarteritis of long duration accompanied by progressive deterioration, in fulminating polyarteritis, in atypical rheumatoid arthritis, and in all cases of arthritis associated with bizarre cutaneous manifestations.

[Although this paper serves to draw attention to the prevalence of arthropathy in the conditions named, the authors' attempts at classification do not advance our knowledge of these diseases or facilitate their diagnosis.]

R. E. Tunbridge.

Some Effects of Nitrogen Mustard and Triethylene Melamine in Acute Disseminated Lupus Erythematosus. ROHN, R. J., and BOND, W. H. (1953). *Amer. J. med. Sci.*, **226**, 179. 2 figs, 18 refs.

As difficulty is often encountered with the use of corticosteroids in the treatment of disseminated lupus erythematosus, five patients at the Indiana University Medical Center, Indianapolis, were treated with nitrogen mustard, and two of them with triethylene melamine as well. The duration of remission of signs and symptoms after administration of these drugs varied from 6 days to a maximum of 217 days, as compared with 14 to 300 days after treatment with ACTH. Since in most of the patients there was impaired bone-marrow function as the result of the disease the total dosage of nitrogen mustard was limited to 0·4 mg./kg. body weight. The authors do not consider that nitrogen mustard and triethylene melamine are effective solely through adrenal cortical stimulation; their mode of action, therefore, must remain speculative. It is suggested that treatment with nitrogen mustard in combination with corticosteroids might be beneficial in these cases.

Geoffrey McComas.

A Nicotinic Acid Ester ("Trafuril") Skin Test in Rheumatic Diseases. [In English.] OKA, M. (1953). *Acta med. scand.*, **145**, 258. 5 refs.

The author reports, from the Hospital of the Rheumatism Foundation, Heinola, Finland, the results of skin tests with "Trafuril" (an ointment containing 5 per cent. tetrahydrofurfuryl nicotinic acid ester) in 269 cases of rheumatism (mainly rheumatoid arthritis) and 69 healthy control subjects. The application of trafuril to the skin resulted in an erythematous reaction within 10 or 15 minutes in all the controls, in the two cases of purpura rheumatica, and in all eight cases of osteo-arthritis. In about two-thirds of the remaining cases (consisting of 228 cases of rheumatoid arthritis, sixteen of ankylosing spondylitis, and two of psoriatic arthritis), the result was negative, a positive reaction occurring mainly in early cases and in children with rheumatoid arthritis. After treatment with ACTH (corticotrophin) or cortisone, or after the development of complications of gold therapy, a positive reaction frequently developed in cases in which it had previously been absent.

Kathleen M. Lawther.

Progressive Systemic Sclerosis (Scleroderma). BEIGELMAN, P. M., GOLDNER, F., and BAYLES, T. B. (1953). *New Engl. J. Med.*, **249**, 45. 7 figs, 30 refs.

In this paper fifteen cases of progressive systemic sclerosis (scleroderma) are described in detail from the Peter Bent Brigham and Robert Breck Brigham Hospitals, Boston. The average age of onset was 40 (range 19 to 52) and all the patients but three were women. All fifteen patients had constitutional symptoms, and showed the characteristic thickening of the skin of the hands. The authors were impressed by the frequent involvement of other systems; for example, twelve had joint pain or swelling, fourteen had cardio-respiratory embarrassment, eleven had gastro-intestinal symptoms. The majority had abnormal signs in the heart and lungs, seven patients showing abnormal chest radiographs in which there was linear streaking at the bases and alteration of the cardiac outline. Electrocardiographic changes were common; these were largely non-specific, and included inverted T-waves, low voltage complexes, and arrhythmias. *Post-mortem* examination of five of the six fatal cases confirmed the widespread visceral changes typified by microscopical fibrosis in the myocardium, lungs, gastro-intestinal tract, kidneys, and liver. Corticotrophin and cortisone therapy was tried in nine cases, but only one patient seemed to benefit. Other treatment with metals, hormone preparations, vitamins, and peripheral vasodilators gave consistently negative results.

The authors suggest that in view of the widespread distribution of the lesions in scleroderma and of the histological findings, this disease must be regarded as an antigen-antibody allergic reaction of the mesenchymal tissues, resembling acute disseminated lupus erythematosus in this respect, but differing from it in its slow response to the allergic reaction and in the predominance of fibrosis and sclerosis. One of the authors' patients presented simultaneously some of the features of both diseases, indicating in their opinion a relationship between the two.

K. C. Robinson.

Treatment of Rheumatoid Arthritis with Phenylbutazone. FREELAND, D., STOREY, G., and THOMPSON, M. (1953). *Lancet*, **1**, 1227. 13 refs.

The authors have investigated at the London Hospital the effect of phenylbutazone ("Butazolidin") in a series of 57 patients suffering from rheumatoid arthritis. Alternate patients were given either phenylbutazone or an inert substance, the dose of phenylbutazone being 200 mg. three times a day for 4 weeks, and neither the patients nor the doctors assessing progress knew which substance each patient was given. Patients were examined before the trial and again after 28 days; subjective improvement was assessed by the relief of pain and joint stiffness and improved ability to perform routine tasks; objective improvement by alterations in the diameter and range of movement of the joints.

The results for 55 patients who completed the course were analysed statistically. The number of patients

showing subjective and objective improvement was significantly greater in the group given phenylbutazone than in the control group, 22 patients receiving phenylbutazone showing subjective improvement as against eleven in the control group, while the figures for objective improvement were twelve and five respectively. No significant change in the haemoglobin values, leucocyte count, or erythrocyte sedimentation rate was noted in those treated with phenylbutazone, and these patients also showed an average gain in weight after 2 and 4 weeks of treatment which was statistically significant. In three patients toxic effects were so severe that treatment with phenylbutazone had to be discontinued.

The effect of the drug on another, larger, but uncontrolled, group of 164 patients is also presented, particular attention being paid to toxic effects. These patients received the drug for periods varying from 1 to 6 months. Toxic effects occurred in 40 per cent. of the cases, and were severe enough in half of these for treatment to be stopped, but in the other half the toxic effects wore off although treatment was continued. The chief complications were indigestion and nausea (28) and skin eruptions (15). Other complications occurring fairly frequently were diarrhoea, sore mouth, oedema, and lymphadenopathy. No case of agranulocytosis occurred. The authors are of the opinion that because of the potential danger of phenylbutazone the drug should be given only under strict medical supervision. *C. E. Quin.*

Toxic Effects of Phenylbutazone, with special reference to Disorders of the Blood. LEONARD, J. C. (1953). *Brit. med. J.*, **1**, 1311. 22 refs.

These two papers both deal with the secondary toxic manifestations of phenylbutazone ("Butazolidin"). In the first, the authors report the occurrence of toxic symptoms in 46 (42 per cent.) of 109 patients with rheumatoid arthritis, osteo-arthritis, or gout, given an average daily dose of 0·6 g. by mouth with restricted salt intake. [This figure is to be compared with the over-all figure of 22 per cent. for cases published in the literature which is cited in the second paper.] Considerable symptomatic improvement was noted in 59 cases, but was unassociated with any reduction in the erythrocyte sedimentation rate. The toxic effects were generally similar to those previously reported and were found to occur usually after 3 weeks of treatment.

The author of the second paper briefly reviews the literature and reports in detail two cases of blood dyscrasia attributable to the drug, one being a case of fulminating aplastic anaemia and the other a case of agranulocytosis with uneventful recovery. There was no evidence that the toxic reactions bore any relation to dosage. In the fatal case, which was diagnosed as one of rheumatoid arthritis, the patient had previously suffered from myxoedema, which had responded to treatment with thyroid, and had also been treated with ACTH (total dose 0·82 g.) and with gold (total dose 0·44 g.). The possibility is discussed that the anaemia might have been due to the previous gold therapy or that the patient had thereby become sensitized to phenylbutazone.
Harry Coke.

Toxic Effects of Phenylbutazone. NASSIM, J. R., and PILKINGTON, T. (1953). *Brit. med. J.*, **1**, 1310. 12 refs.

Fatal Agranulocytosis and Gastric Ulceration due to Phenylbutazone. DILLING, N. V. (1953). *Lancet*, **1**, 1230. 19 refs.

A Clinical Study of Phenylbutazone ("Butazolidin") in Various Types of Arthritis. PLATOFF, G. E. (1953). *J. Mich. med. Soc.*, **52**, 980. 21 refs.

Phenylbutazone: An Evaluation. SNOW, W. G. (1953). *Calif. Med.*, **79**, 211. 27 refs.

Recent Investigations on Phenylbutazone. An Experimental Study. (Ulteriori indagini sul fenilbutazone. Studio sperimentale riguardante la sua eliminazione nelle orine e nei liquidi organici ed il comportamento del "test dell'uropepsina".) LUCHERINI, T., NATALE, P., CONESTABILE, E., and CERIMELE, E. (1953). *Reumatismo*, **5**, 303. 5 figs, 5 refs.

Evaluation of Certain Newer Products in Arthritis Therapy. GRAY, J. W., and MERRICK, E. Z. (1953). *J. med. Soc. N.J.*, **50**, 456. 2 figs, 1 ref.

Treatment of Chronic Joint Disease with "GT 50" (Vitamin D_2). (Le traitement des arthroses par le GT 50.) GAUTIER, A. (1953). *Praxis*, **42**, 709. 3 refs.

Impact of Adrenal Hormones on the Treatment of Arthritis. ROBINSON, D. (1953). *Canad. med. Ass. J.*, **69**, 486.

Amidopyrin Gentisate in the Treatment of Rheumatism. (Il gentisato di amidopirina nella terapia antireumatica.) CERIMELE, E. (1953). *Minerva med.* (*Torino*), **44**, 713. 9 refs.

Investigations into the Mode of Action of Salicylic Acid and Amidopyrin. (Untersuchungen über den Wirkungsmechanismus der Salizylsäure und des Amidopyrins.) STEPANTSCHITZ, G., KRESBACH, E., and MAYERHOFER, F. (1953). *Klin. Med.* (*Wien*), **8**, 466. 22 refs.

Observations on the Use of Chloro-amines in the Treatment of Bronchial Asthma and Rheumatoid Arthritis. (Osservazioni sull'uso delle cloroamine nella terapia dell'asma bronchiale a dell'artrite reumatoide.) MALAGUZZI VALERI, C., and RAIMONDO, F. DI (1953). *Minerva med.* (*Torino*), **44**, 1329. Bibl.

Heparin and Heparinoid Toxin in the Pathogenesis of Hyperfibrinogenemia in Chronic Arthritis. PETERMAN, E. A. (1953). *J. Mich. med. Soc.*, **52**, 970. 2 figs, 9 refs.

Effect of Placental Thromboplastin on Hyperfibrinogenemia in Rheumatic Disease. PETERMAN, E. A. (1953.) *J. Mich. med. Soc.*, **52**, 977. 5 refs.

Chronic Arthritis in Children. (Chronické arthritidy ve věku dětskem.) HOUŠTĚK, J., and SRBOVÁ, D. (1953). *Pediat. Listy*, **8**, 256. 2 figs, 20 refs.

Direct Auscultation of the Joints. Preliminary Clinical Observations. PEYLAN, A. (1953). *Rheumatism*, **9**, 77. 2 figs, 6 refs.

Reiter's Disease. (Doença de Reiter.) GIARDULLI, A. (1952). *Rev. brasil. Oftal.*, **10**, 219. 20 refs. Also (1952) *Patologia Ocular*, **1**, 115. 20 refs.

Monarticular and Destructive Arthropathy in Reiter's Syndrome. GUCK, J. K., and WOLF, J. (1952). *Amer. J. Sci.*, **224**, 653.

Nonsyphilitic Interstitial Keratitis and Bilateral Deafness (Cogan's Syndrome) associated with Essential Polyangitis (Periarteritis Nodosa). A Review of the Syndrome with consideration of a Possible Pathogenic Mechanism. OLINER, L., TAUBENHAUS, M., SHAPIRA, T. M., and LESHIN, N. (1953). *New Engl. J. Med.*, **248**, 1001. 3 figs, 47 refs.

Relationship between Periarthritis Nodosa and Rheumatism. (Sui rapporti fra panarterite nodosa e reumatismo.) CANDIANI, G. (1953). *Riv. Anat. patol.*, **7**, 257. 2 figs, bibl.

Stevens-Johnson Syndrome. HAAS, W. R., BIRENBAUM, A., and KAMINESTER, C. E. (1952). *U.S. armed Forces med. J.*, **3**, 1431.

Stevens-Johnson Syndrome; Stomatitis, Conjunctivitis, Erythema Exudativum Multiforme. (Syndroom van Stevens-Johnson: stomatitis, conjunctivitis, erythema exsudativum multiforme.) HOLLEVOET, —. (1952). *Ann. belg. Méd. milit.*, **105**, 64.

Stevens-Johnson Syndrome, a Variant of Erythema Multiforme Exudativum, treated with Aureomycin. HARMSTON, G. J. (1952). *Rocky Mtn. med. J.*, **49**, 931.

Disk Syndrome

Lumbar Disk Lesion Syndrome. ARMSTRONG, J. R. (1953). *Rheumatism*, **9**, 82.

Cervical Spondylitis as a Cause of Cervicobrachial Pain. (La cérvicoartrosis en las algias cérvicobraquiales.) BOSCH OLIVES, V. (1953). *Rev. esp. Reum.*, **5**, 81.

Sciatica and Dilatation of the Epidural Veins. (Sciatique et dilatation des veines epidurales.) WERTHEIMER, P., RAVAULT, P., VIGNON, G., and MICHEL, R. (1953). *J. Méd. Lyon*, **34**, 877.

Gout

Studies in Gout, with particular reference to the Value of Sodium Salicylate in Treatment. MARSON, F. G. W. (1953). *Quart. J. Med.*, **22**, 331. 6 figs, 33 refs.

The author reviews the literature relating to the importance of urate deposition in chronic gout and of the reduction of the serum uric acid level in its treatment, and discusses the two available approaches to the therapeutic problem—by restriction of diet, and by the reduction of tubular reabsorption of urates in the kidneys by means of certain drugs, with particular reference to sodium salicylate.

He then describes the results of investigations carried out at the General Hospital, Birmingham, on 32 patients with chronic gout which had persisted for at least 3 months and was unrelieved by colchicine therapy. The effect of diet on the serum uric acid level was studied in eight male patients who received alternately low- and high-purine diets, each for a period of 7 to 11 days. In seven of the eight patients the change from a low- to a high-purine diet was accompanied by a rise in the serum uric acid level, but the change was slight in degree and insufficient, in the author's opinion, for a low-purine diet of therapeutic value.

Continuous sodium salicylate therapy in a daily dosage of 60 to 140 gr. (4 to 9 g.) was then attempted in 29 cases and was maintained in fourteen of them for more than a year. In only one case did it prove impossible to reduce the serum uric acid level to within normal limits, and this patient was the only one with severe renal impairment. Intermittent treatment (for three consecutive days in each week) failed to maintain the reduction. All the patients experienced marked subjective improvement while receiving salicylates. In a few cases improvement was delayed for several weeks, but once started it was progressive. Reduction in the size of tophi took place, and in two instances tophi disappeared completely. Marked radiological improvement was observed in four cases. The maintenance of the serum uric acid content at a normal level did not necessarily prevent the occurrence of acute gouty attacks, for which colchicine was prescribed and usually afforded relief. Symptoms of salicylism usually appeared on starting treatment, but in most cases good tolerance developed after the first month. No haemorrhagic manifestations were observed, vitamin K being given when the plasma prothrombin concentration, which was estimated at frequent intervals, fell below 25 per cent. of normal.

The author claims to have shown very conclusively that continuous administration of sodium salicylate, in the absence of nephritis, can lower the serum uric acid level in chronic gout and thus ameliorate the symptoms and reduce the disability. *R. E. Tunbridge.*

Two Cases of Gouty Iritis. (L'iritis goutteuse. A propos de deux observations.) BONAMOUR, G. (1953). *Bull. Soc. ophthal. Franç.*, No. 4, 413.

This type of iritis is always unilateral and is of marked onset. The signs are deep and acute and the anterior chamber is filled with exudates and blood. Treatment with colchicin gives complete and rapid recovery. *J. Rougier.*

Conjunctival Tophi associated with Gout. YOURISH, N. (1953). *Arch. Ophthal. (Chicago)*, **50**, 370. 1 fig., 7 refs.

In a known case of gout, fine needle-like crystals were seen in the bulbar conjunctivae in the inter-palpebral zones. The deposits, which were asymptomatic, were proved to be urate salts by biopsy and the murexide test. *Redmond Smith.*

Treatment of Acute Gout with Butazolidin. (Tratamiento del ataque agudo de gota por butazolidina.) BARCELÓ, P., SANS SOLÁ, L., and SERRA, A. PERALBA (1953). *Rev. esp. Reum.*, **5**, 61.

Gouty Arthritis. Diagnosis and Treatment. SIGLER, J. W., and ENSIGN, D. C. (1953). *J. Mich. med. Soc.*, **52**, 959. 4 figs.

Diagnosis and Treatment of Gouty Arthritis. TALBOTT, J. H. (1953). *Calif. Med.*, **79**, 220. 11 refs.

Statistical Analysis of 252 Cases of Gout. (Consideraciones estadísticas sobre 252 casos de gota.) BARCELÓ, P., and SANS SOLÁ, L. (1953). *Rev. esp. Reum.*, **5**, 64.

General Pathology

Serum Complement in Children with "Collagen Diseases". WEDGWOOD, R. J. P., and JANEWAY, C. A. (1953). *Pediatrics*, **11**, 569. 8 figs, 27 refs.

The authors give details of a new spectrophotometric method developed at the Children's Medical Center (Harvard Medical School), Boston, for the determination of a 50 per cent.-haemolytic end-point in the estimation of serum complement. Using this technique, which they consider to be far more sensitive than the normal routine methods at present in use, they studied the quantitative changes in serum complement level in seventy children suffering from various collagen diseases. The initial figures were below normal in lupus erythematosus (4), acute glomerular nephritis (20), and nephrosis (15), and greater than normal in anaphylactoid purpura (14), dermatomyositis (6), and rheumatoid arthritis (11). In the three disorders in which the serum complement value was initially low, a rise occurred in association with clinical improvement, however induced. There was no evidence of anti-complementary activity in the serum. The low serum complement level before treatment cannot be explained as the result of protein loss during the acute phase, as there is no correlation between the degree of urinary protein excretion and the serum complement level, and would appear to support the theory that these diseases are allergic in nature, serum complement being depleted by certain gross antibody-antigen reactions. The significance of the high serum complement values in rheumatoid arthritis, dermatomyositis and rheumatic fever is discussed, and it is suggested that such findings do not exclude the possibility of an immunological mechanism in the pathogenesis of these diseases; the differences in serum complement titres may reflect differences in the relative quantities, types, or location of the antigens and antibodies involved, or in the time relation between stimulus and reaction. *R. E. Tunbridge.*

Pathogenesis of the Rheumatic Granuloma. (Zur Pathogenese des rheumatischen Granuloms.) ALBERTINI, A. VON (1953). *Schweiz. med. Wschr.*, **83**, 772. 6 figs, 31 refs.

On the basis of observations made at the Institute of Histopathology, University of Zürich, the author considers that the primary lesion in the Aschoff body in rheumatic myocarditis is tissue necrosis, and that this necrosis may occur not only in connective tissue, but also in muscle fibres. The cellular reaction which develops for the reabsorption of these necroses consists mainly of basophil histiocytes, which may be converted into Anitschkow cells. These Anitschkow cells are not myocytes—for besides being seen in the myocardium they also occur in the endocardium and epicardium—but are the form taken by basophil histiocytes in the heart (to which Anitschkow cells appear to be limited) in rheumatism and endocarditis lenta, and in the healing of experimental wounds of the heart and of cardiac infarcts.

The structure of the granuloma, however, provides no evidence regarding its cause, but it is suggested that streptococcal infections and associated allergic factors may be responsible. *C. L. Oakley.*

Chemical Examination of Connective Tissue in Rheumatic Fever. CONSDEN, R., GLYNN, L. E., and STANIER, W. M. (1953). *Biochem. J.*, **55**, 248. 1 fig., 33 refs.

Subcutaneous nodules were excised from the elbow region in twelve cases of rheumatic fever at the Canadian Red Cross Memorial Hospital, Taplow, freed by microdissection from adjacent tissue, washed, dried, and extracted with benzene and light petroleum to remove fatty material. Specimens of normal connective tissue obtained post mortem were treated similarly. (The authors give full details of all methods.) After autoclaving with water at 120° C. for 3 hours to remove collagen, the rheumatic nodules yielded a residue varying between 25 and 40 per cent. of the original weight, whereas the residue from non-rheumatic connective tissue gave only 10 per cent. residue. The extracts of the two tissues thus obtained, after hydrolysis with hydrochloric acid, gave similar chromatograms which resembled those obtained by Bowes and Kenten (1949) for collagen. The chromatograms of the residues, however, differed markedly, those from non-rheumatic connective tissue yielding findings suggestive of elastin, while those from the rheumatic-nodule residues suggested the presence of tyrosine-rich protein or polypeptide in addition to elastin; this substance appeared to be present also in non-rheumatic tissue, but in much smaller amount. Analysis of the sugars released on hydrolysis suggested that the polysaccharide components normally present in subcutaneous connective tissue are also present in rheumatic nodules, but in greater quantities. The higher content of non-collagen protein and of polysaccharide in the nodules may be due either to increased deposition of these substances or to the destruction and removal of collagen. The presence of a tyrosine-rich protein and of polysaccharide in both rheumatic and non-rheumatic tissue indicates the presence of substances other than collagen and elastin, possibly forming part of the interfibrillary ground substance, which is generally considered to be mucoprotein in nature. There was no evidence of the presence of large quantities of fibrin in the nodules.

R. E. Tunbridge.

Assessment of Adrenocortical Activity by Assay of 17-Ketogenic Steroids in Urine. NORYMBERSKI, J. K., STUBBS, R. D., and WEST, H. F. (1953). *Lancet*, **1**, 1276. 8 figs, 42 refs.

This paper from the Centre for the Investigation of Rheumatic Diseases, Nether Edge Hospital, Sheffield, describes a method for estimating urinary steroids derived from the adrenal cortex. Certain corticosteroids (17 : 20 : 21-triols and 17 : 20-glycols) on oxidation with periodic acid yield 17-ketosteroids which can be easily estimated; this procedure is in general use. Norymberski has shown that by substituting sodium bismuthate for periodate as the oxidizing agent it is possible to extend the estimation of these 17-ketogenic steroids to include corticosteroids with a dihydroxyacetone side-chain (17 : 21-diol-20-one). In the present paper the term "17-ketogenic steroids" is used to denote these converted by bismuthate (not by periodate) into 17-ketosteroids. Urine 24-hour samples, collected without preservative and diluted with distilled water up to 2 l., were assayed in duplicate for 17-ketosteroids and for "total 17-ketosteroids" (after bismuthate oxidation), the difference between the two levels representing the 17-ketosteroids derived from 17-ketogenic steroids on oxidation. The experimental procedure was adapted from that of Drekter and others (*J. clin. Endocr.*, 1952, **12**, 55), and has been fully described in a previous paper (Norymberski, *Nature (Lond.)*, 1952, **170**, 1074). By this method the recovery of added corticosteroid is 80 per cent. or more.

The output of 17-ketogenic steroids of normal men and women, and of children, was determined and compared with that of patients with various diseases. In cases of rheumatoid arthritis and ankylosing spondylitis the output was about 40 per cent. lower than in normal adults; treatment with ACTH caused increased output, which varied irregularly with dose and subject. In patients treated with cortisone acetate there was a linear relation between the size of dose and the excretion of 17-ketogenic steroids, indicating that the assay of the latter gives a measure of adrenal activity, 17α-hydroxycorticosterone, the main cortical steroid, being probably excreted as a dihydroxyacetone derivative.

This simple method has the great advantage that it does not require hydrolysis by strong acid, thereby avoiding destruction of corticosteroids. *Nancy Gough.*

Group-A Polysaccharide Precipitin Reactions in Acute Streptococcosis and Rheumatic Fever. WEINSTEIN, L. (1953). *Yale J. Biol. Med.*, **25**, 349. 11 refs.

After a review of previous work on the significance of the presence in the serum of antibodies to group specific streptococcal polysaccharides in the rheumatic diseases, the author details his own findings at the Massachusetts Memorial Hospitals (Boston University School of Medicine) in sera from 151 patients with streptococcal infections, 76 patients with acute rheumatic fever, and 310 patients with other diseases. The precipitating antibody for purified group-A carbohydrate was detected by layering the bacterial extract over the serum and incubating at 37° C. for 2 hours and then transferring to a refrigerator. Readings were made at 24, 48, and 72 hours, control tubes being set up containing bacterial extract and saline or serum and saline. (The details of preparation of the bacterial extract containing group specific polysaccharide are given in full.) Serum was obtained from each patient at the time of admission and again 14 days later. A positive precipitin reaction was obtained in 34 per cent. of the group with streptococcal infections (without non-suppurative complications), in 24 per cent. of the group with acute rheumatic fever, and in proportions ranging from 0 to 100 per cent. in the various other diseases. These results are somewhat at variance with other published results, possibly owing to the author's method of purification of the extract, which is simpler than that usually employed but is claimed to be more efficient. The extract was free from type specific nucleoprotein, since there was no precipitation with potent type-3 specific antiserum.

The author concludes that antibody may frequently be present in a patient's serum without other evidence of streptococcal infection, that its absence does not exclude the presence of streptococcal infection or rheumatic fever, and that hypersensitization to group-A specific polysaccharide is of no significance in the pathogenesis of the rheumatic state. *E. G. L. Bywaters.*

Antistreptolysin-O Serum Levels. Their Determination and Use as a Diagnostic Aid with particular reference to Active Rheumatic Fever in Children. HOLLINGER, N. F. (1953). *Amer. J. publ. Hlth*, **43**, 561. 1 fig., 32 refs.

Comparisons of the mean titre of antistreptolysin-O (AST) in the serum of non-rheumatic children and of children with active rheumatic fever have not hitherto revealed differences sufficiently great to provide a reliable diagnostic test, although a low or absent AST may provide confirmatory evidence of the absence of active rheumatic fever. The present author, working at the University of California, attempted to discover whether a minimum titre could be established to provide a "diagnostic exclusion index". Serum was therefore obtained from individuals under 21 years of age who were classified after examination (at a number of centres) as follows: 2,147 normal children; 2,988 with illness other than active rheumatic fever; 197 with active rheumatic fever. AST determinations were made by the technique of Rantz and Randall (1945), using stable, reduced, desiccated streptolysin-O, a number of different laboratories participating in the work. The reproducibility of results as between laboratories was tested and found satisfactory.

In all three groups there was a significant degree of variation in titre between sera from different parts of the United States. Nevertheless, analysis of the combined results for non-rheumatic subjects showed that in all but one of the geographical areas at least 30 per cent. of sera gave AST values of less than 100 units per ml., whereas less than 5 per cent. of sera from cases of active rheumatic fever gave AST values in this range. The author notes that of the AST values in 1,142 cases of rheumatic fever reported in the literature, all but two were above the level of 50 units per ml. He therefore suggests that a titre of 50 units or less per ml. obtained repeatedly in the

same case is a highly reliable "exclusion index" for rheumatic fever.

[It is not clear from the text whether in selecting the cases of active rheumatic fever the duration of the disease was taken into consideration. If cases with activity of long duration were included, these results must be taken to support Coburn's original view that a rise in serum antistreptolysin titre is directly related to the activity of the disease.] *E. J. Holborow.*

Vascularity of the Early Subcutaneous Nodule of Rheumatoid Arthritis. SOKOLOFF, L., MCCLUSKEY, R. T., and BUNIM, J. J. (1953). *Arch. Path.* (*Chicago*), **55**, 475. 10 figs, 16 refs.

The structure of the early subcutaneous nodule of rheumatoid arthritis was studied at the New York University and the Bellevue Hospital. It is postulated that one of the primary morphological changes in rheumatoid arthritis is an arteritis and that the developing nodule, evoked probably by trauma, is seen microscopically as an active localized proliferation of the involved blood vessels with, spreading out from them, a granulation tissue in which there appears necrosis of the fibres and a reactive cellular response (palisades). The process is thought to be centrifugal, possibly due to a toxic effect from the vessels, the nodule differing from that of acute rheumatic disease only in the greater degree of necrosis. *A. C. Lendrum.*

Research into the Presence of a Haemagglutinating Factor in the Serum in Cases of Rheumatoid Arthritis. (Ricerche sulla presenza di un fattore emoagglutinante nel siero di malati di poliatrite cronica primaria.) CARCASSI, U. (1953). *Rif. med.*, **67**, 1253. 36 refs.

Antistreptolysin Titre of Patients in a Children's Hospital. (Antistreptolysintitern bland patienterna på ett barnsjukhus.) WASZ-HOCKERT, O., and WIDHOLM, O. (1953). *Nord. Med.*, **50**, 1665. 11 refs.

Serological Researches in Chronic Rheumatism. (Recherches sérologiques dans les rhumatismes chroniques inflammatoires.) JACQUELINE, F., EYQUEM, A., and JOCHEM, E. (1953). *Rev. Rhum.*, **20**, 617. 1 fig.

Liver Function in Rheumatoid Arthritis. (Beitrag zur Leberfunktion bei der primär chronischen Polyarthritis.) SCHMID, J. (1953). *Med. Klin.*, **48**, 1322. 34 refs.

Liver Changes in Rheumatic Diseases. (Leberveränderungen bei rheumatischen Krankheiten). TRUTSCHEL, W., and FRÖLICH, D. (1953). *Münch. med. Wschr.*, **95**, 1251. 1 fig., 6 refs.

Laboratory Tests for Rheumatoid Arthritis. WELLS, B. B. (1953). *Rheumatism*, **9**, 87.

ACTH, Cortisone, and Other Steroids

Local Injection of Hydrocortisone and Cortisone into Skin Lesions of Sarcoidosis. SULLIVAN, R. D., MAYCOCK, R. L., JONES, R., and BEERMAN, H. (1953). *J. Amer. med. Ass.*, **152**, 308. 3 figs, 11 refs.

In an attempt to demonstrate the action of hydrocortisone and cortisone on the skin lesions of sarcoidosis five patients at the Hospital of the University of Pennsylvania with histologically proven sarcoidosis of 2 to 11 years' duration received local injections of these substances in close proximity to cutaneous sarcoid lesions. Injection of 2·5 mg. hydrocortisone into eighteen lesions resulted in initial regression in 3 to 7 days and complete or nearly complete resolution in 14 days. In three patients ten lesions recurred within 4 to 7 weeks of the injection, but they were one-third smaller than before treatment. In two patients in whom five lesions were treated there was no evidence of recurrence 4 to 14 weeks later, at which time administration of cortisone by mouth was begun.

Examination of biopsy specimens of the treated lesions 7 days after the infiltration revealed typical sarcoid granulomata; examination 14 days after the treatment showed no residuum of the sarcoid lesions. The most striking histological finding was the presence in the corium of basophilic granular material, subsequently shown to be hydrocortisone acetate, around which there was no cellular reaction.

Injection of cortisone resulted in a similar but less striking regression of the lesions. There was no change in skin lesions not subjected to local infiltration of hydrocortisone or cortisone, and less concentrated preparations resulted.

After this part of the investigation was completed, four patients were given 25 mg. cortisone by mouth four times daily for 6 weeks. In 1 to 2 weeks the skin lesions began to diminish in size until at 4 to 6 weeks resolution was about two-thirds complete. Two weeks after cessation of treatment all the skin lesions began to relapse, and in three of the four patients numerous new lesions appeared; this was considered to be a "rebound" phenomenon.

It is concluded that in selected cases local administration of hydrocortisone may influence the course of cutaneous sarcoidosis. *D. W. Barritt.*

Hydrocortisone and Inflammatory Rheumatism. (Hydrocortisone et rhumatismes inflammatoires.) SÈZE, S. DE, ROBIN, J., and DEBEYRE, N. (1953). *Rev. Rhum.*, **20**, 298.

The authors report their results in a preliminary trial at the Hôpital Lariboisière, Paris, of hydrocortisone injected intra-articularly in 24 patients with rheumatoid arthritis, of whom nineteen were already undergoing treatment with cortisone. Their observations suggest that the maintenance dose of cortisone may be considerably reduced if one or more joints in which active disease is persisting are treated locally with hydrocortisone. In fifteen patients given intra-articular injections of hydrocortisone the pain, swelling, and stiffness diminished and sometimes disappeared, and in all of them it was possible to reduce the maintenance dose of cortisone without

relapse. In one patient with ankylosing spondylitis accompanied by arthritis of a hip-joint, local treatment of the hip brought rapid relief, and it was found possible to reduce the maintenance dose of cortisone from 125 to 75 mg. *Kenneth Stone.*

Therapeutic Effect of Intra-Articular Hydrocortisone Acetate. (130 Cases of Inflammatory and Degenerative Rheumatism.) (De l'effet thérapeutique de l'hydrocortisone-acétate intra-articulaire. (Rapport sur une thérapeutique de 130 cas de rhumatisme inflammatoire et dégénératif.)) PAP, L. DE, and TEIXEIRA, M. A. (1953). *Rev. Rhum.*, **20**, 285. 3 figs, 11 refs.

The effect of the intra-articular injection of cortisone is uncertain and transitory. Although hydrocortisone (Kendall's Compound F) has the same therapeutic properties as cortisone it is unexpectedly efficacious when applied locally. The authors report their results in 130 patients at the Instituta Reumatologia, Lisbon, suffering from a wide variety of rheumatic diseases, principally rheumatoid arthritis and osteo-arthritis, and treated with hydrocortisone. The most effective dose for injection of large joints was found to be 25 mg., and for smaller joints 8 to 15 mg.

In cases of rheumatoid arthritis the inflammatory signs disappeared first; in some cases relief of pain, easier though restricted movement, and reduction in swelling lasted up to 3 weeks, but lessened after 7 to 10 days. In osteo-arthritis the relief was more lasting. The return of symptoms is the deciding factor as to whether, and when, injections are to be repeated. In general, they were given weekly in rheumatoid arthritis. The authors stress that the secret of success is that the injections shall be truly intra-articular, particularly in affections of the hip-joint; the technique is described in some detail. No generalized effects were noted, the action of the hormone appearing to be purely local: for instance, in no case was improvement in a polyarthritis observed, except in the joint treated.

The effect of hydrocortisone is not specific, as disorders of the most varied aetiology, such as traumatic conditions, osteo-arthritis, rheumatoid arthritis, rheumatic fever, tenosynovitis, and sciatica respond equally well. In the 37 cases of rheumatoid arthritis, all signs of activity of the disease disappeared in six patients after six to eight injections; 29 patients were improved, and only two were unaffected. Improvement followed in all of 28 cases of osteo-arthritis of the knee, and was good but less satisfactory in seventeen cases of osteo-arthritis of the hip. The authors point out that this therapy is not curative; relief of pain in an osteo-arthritic knee, even for several months, does not imply cure, for the same morbid process continues; and in rheumatoid arthritis symptoms recur sooner or later, when the injections of hydrocortisone are stopped. *Kenneth Stone.*

Local Injection of Hydrocortisone in Articular and So-called Para-Articular Rheumatism. (L'hydrocortisone en injection *in situ* dans les arthroses et les affections dites para-articulaires rhumatismales.) SÈZE, S. DE, ROBIN, J., and DENIS, A. (1953). *Rev. Rhum.*, **20**, 303.

In this series of 87 patients with rheumatic diseases treated at the Hôpital Lariboisière, Paris, by intra-articular injections of hydrocortisone, the dose at each injection was 25 mg. and injections were given once weekly at first.

In 25 patients with osteo-arthritis of the knee the results were very good or good in seventeen (68 per cent.). In five of these, one, two, or three injections brought amelioration lasting 1 to 2 months. In the eight cases showing a less satisfactory response, pain returned after each injection in from 1 to 3 weeks. In a group of 25 patients with osteo-arthritis of the hip, the results were less striking, but fourteen cases (56 per cent.) were relieved. One patient obtained lasting relief after five injections; in others, relief after each injection lasted only 3 or 4 weeks. Hydrocortisone was also given to 21 patients with scapulo-humeral peri-arthritis. In cases with acute or subacute sub-acromial bursitis in which pain was the predominant feature, the effect was in every case excellent. It was less good in conditions of long duration in which there was much restriction of movement owing to adhesions. *Kenneth Stone.*

Practical Experience with Hydrocortisone. (Praktische Erfahrungen mit Hydrocortisone,) BÖNI, A. (1953). *Praxis*, **42**, 702. 4 refs.

After quoting the results claimed by other workers in the treatment of chronic articular rheumatism with intra-articular hydrocortisone, the author reports his own experience at the Institute for Physical Therapy of the University of Zürich in eighteen cases of rheumatoid arthritis. The dose of hydrocortisone given at each injection was 5 mg. for finger and toe joints, 10 mg. for the hands and feet, 20 mg. for the elbow, 20 to 30 mg. for the shoulder, and 40 to 50 mg. for the knee. However, no attempt was made at local treatment until the general health of the patient had been improved as far as possible by other means, such as blood transfusion, gold injections, and administration of cortisone, and only those joints which did not yield to these general measures were injected with hydrocortisone.

A detailed analysis of the results is difficult in view of the polytherapy used, but several individual cases are described. In general, relief of pain and swelling resulted from the injection, enabling effective physiotherapy to be carried out. Injections had to be repeated at intervals of 10 to 14 days, though the interval could usually be gradually extended. Some patients were fortunate in that the local inflammatory reaction cleared up after only one or two injections, but in one case quoted, 105 injections into eight joints were required.

In the opinion of the author, the intra-articular injection of hydrocortisone by itself is not enough, its effect being entirely local. *D. Preiskel.*

How Does Sodium Salicylate Act? (Comment agit le salicylate de sodium?) COSTE, F., BOUREL, M., DELBARRE, F., and WEISSENBACH, R. (1953). *Presse méd.*, **61**, 979. 4 figs, 32 refs.

Historical considerations show that sodium salicylate has always in the past been held to act in accordance with the currently accepted theory of the aetiology of

rheumatism. Thus it is not surprising that the discovery of the effect of cortisone in rheumatoid arthritis was soon followed by reports of the development of Cushing's syndrome, of reduction in the peripheral eosinophil leucocyte count, and of changes in urinary 17-ketosteroid excretion in patients receiving large doses of salicylates, while work on experimental animals confirmed that salicylates had certain cortisone-like properties.

However, it is probable that these effects of salicylates result from a purely non-specific stimulation of the pituitary-adrenal axis, since many other substances (collectively described by Selye as "non-specific stressor agents" and including ephedrine, colchicine, atropine, urethane, nitrogen mustards, and others) have a similar action, although most of them are completely ineffective in the treatment of the rheumatic diseases. Sodium salicylate must therefore have a specific anti-rheumatic action in addition to any such non-specific effect on the endocrine glands.

This thesis is supported by the results of experiments carried out by the authors at the Rheumatological Clinic of the Faculty of Medicine of Paris. It was confirmed that sodium salicylate has a direct corticotrophic action, but this was shown to be far too feeble to be responsible for its therapeutic efficacy, the depletion of adrenal ascorbic acid caused by clinically effective doses of salicylate being far less than that resulting from therapeutically effective doses of ACTH. Again, whereas quite small doses of ACTH or cortisone definitely increased urinary corticosteroid excretion in five healthy subjects, large doses of sodium salicylate had no demonstrable effect. It must thus be concluded that, although sodium salicylate has an undoubted stimulant action on the pituitary-adrenal axis, the mechanism by which it exerts its specific therapeutic effect remains unknown.

Adrian V. Adams.

Prevention with Testosterone of Adrenal Atrophy resulting from Cortisone Therapy. (La prophylaxie par la testostérone, de l'atrophie surrénalienne provoquée par les traitements a la cortisone.) TURIAF, J., ZIZINE, L., and JEANJEAN, Y. (1953). *Presse méd.*, **61**, 825. 32 refs.

When rats weighing 80 to 100 g. are given daily injections of approximately 2 mg. cortisone they develop adrenal atrophy in 8 to 10 days—as after hypophysectomy. If, however, a similar quantity of testosterone is given together with the cortisone, the atrophy is prevented. Adrenal atrophy after prolonged cortisone administration is not unknown in human subjects, and several cases have been reported in which the condition has been fully confirmed *post mortem*. Fortunately, warning of the development of this atrophy can be obtained in the live patient by means of Thorn's test (which was used in this study to evaluate the effect of testosterone) and the cortisone omitted, if necessary, in order to allow the adrenal cortex to recover. It has been customary to give ACTH (corticotrophin) for a period in such cases before reverting again to cortisone; in the opinion of the authors this is unnecessary if testosterone (acetate or propionate) is given at intervals during the administration of cortisone. The quantity they used in a series of cases described here was small (25 mg. weekly); it caused no side-effects and was equally efficacious in both men and women.

The patients were divided into four groups:

(1) Six patients were treated with cortisone alone, and Thorn's test revealed adrenal insufficiency in five after only 1·5 g. cortisone had been given;

(2) Twelve patients received cortisone plus testosterone, and in half the cases adrenal function appeared to be unaffected;

(3) Five patients who had been treated with cortisone alone and showed suppression of adrenal function were now given testosterone with cortisone, and it was found that in three of them normal function was restored;

(4) Two patients had been receiving both hormones; testosterone was omitted and cortisone continued alone, Thorn's test subsequently indicating adrenal damage.

The evidence suggests that testosterone exerts a protective effect. There is some evidence, also, that it counteracts the electrolyte disturbances caused by cortisone. The number of cases treated is small but the results obtained are sufficiently promising to justify more extensive trials.

D. Preiskel.

Influence of ACTH and Cortisone on Experimental Antibody Production in Rabbits. MOESCHLIN, S., BÁGUENA, R., and BÁGUENA, J. (1953). *Int. Arch. Allergy*, **4**, 83. 2 figs, 18 refs.

A number of workers in recent years have been concerned with the influence of ACTH (corticotrophin) and cortisone on antibody production in experimental animals. The present authors, continuing their studies on plasma-cell development during antibody formation, now describe the results of their investigation, carried out at the University of Zürich, of the influence of ACTH and cortisone on these responses in the rabbit. Previously, they had shown that antibody formation could be related to plasma-cell response in the spleen of rabbits and, in common with other workers, that administration of ACTH and cortisone could depress the formation of antibody in rabbits undergoing immunization against certain antigens. The present experiments were planned to obtain more detailed information about the effect of these substances on the antibody and plasma-cell response of rabbits, the immunizing agent used being a polyvalent typhoid-paratyphoid vaccine. [This was presumably of the heat-killed phenol-preserved type, since the antibody response was measured by the paratyphoid BH serum agglutinin titre. Precise details of the agglutination technique are not given, nor do the authors state whether the agglutinable suspension used for the test was a standardized monophasic suspension or a simple diphasic killed broth culture.]

The animals were first sensitized with an injection of the polyvalent vaccine, and after irregular intervals (generally about 3 weeks) they were re-injected with the vaccine, given intravenously. The treated animals received either cortisone or ACTH for varying periods and at different intervals in relation to the re-injected vaccine in the several series of experiments. Blood tests were made before re-injection, and finally the animals

were bled out at different stated intervals, killed, and plasma-cell counts carried out on spleen smears; the same procedure was followed in the control animals, and the agglutinin response and plasma-cell counts were compared in the two groups.

In general, the authors showed that ACTH or cortisone, given either 2 hours or 10 minutes before, or simultaneously with, the intravenous re-injection of the vaccine, had little or no effect on the antibody or plasma-cell response. When, however, the hormones were given 7 days before the re-injection of the vaccine, there was a marked decrease in antibody production, and also a reduction in the absolute number of plasma cells in the spleen. [These findings are shown in two series of graphs, but it is difficult to follow the detailed results as given in various Tables.] *H. J. Bensted.*

Histological and Histochemical Study of Granulation Tissue under the Influence of Tissue Therapy. Comparison with the Action of Cortisone. (Étude histologique et histochimique du tissu de granulation sous l'influence de la thérapeutique tissulaire. Comparaison avec l'action de la cortisone.) BOISTESSELIN, R. DU, and BRUX, J. DE (1953). *Presse méd.*, **61**, 543. 3 figs, 14 refs.

Although there have been many reports of the clinical effects of Filatov's tissue therapy, there have been few histochemical studies. In this study, carried out in the Department of Pathological Anatomy, Hôpital Boucicaut, Paris, two groups of male white rats received implants of an inert material ("spongel") under the muscular wall of the abdomen, the second group being given in addition three injections of 25 mg. cortisone in the course of one week; in a third group of animals the implant consisted of dried placenta. One animal from each group was then killed each week and the implants were investigated macroscopically and microscopically, specific stains for collagen, reticulin, amyloid, mucoid, and mucopolysaccharides being employed. The testicles and adrenal glands were also examined.

There was no hard fibrous tissue around the implant in the animals given cortisone, or in the group receiving the implant of placenta tissue, the two groups differing only in that the placental implants produced more blood vessels and, histochemically, a high concentration of mucopolysaccharides. In the cortisone-treated group the adrenal glands showed cortical atrophy, but in none of the three groups was there a change in the testicles. The authors suggest that placental tissue contains a principle which activates the proliferation of fibroblasts. *H. Lehmann.*

Effect of ACTH and Cortisone on Vitamin-C Metabolism and on the Weight and Composition of the Liver in Guinea-pigs and Other Species. HARRIS, L. J., BLAND, M. N., HUGHES, R. E., and CONSTABLE, B. J. (1953). *Lancet*, **1**, 1021. 5 figs, 1 ref.

The inter-relationship of adrenal function and vitamin-C metabolism was studied in a series of experiments carried out in the Dunn Nutritional Laboratory, Cambridge, in which an intramuscular injection of 2 mg. ACTH was given to guinea-pigs four times a day. The animals were not hypophysectomized.

Although the concentration of ascorbic acid in the liver and adrenal glands was diminished, the total quantity present was not affected, since the organs themselves became enlarged. Administration of ACTH did not hasten the onset of scurvy in guinea-pigs given a diet deficient in ascorbic acid, nor did it increase the rate of depletion of ascorbic acid from the liver or the adrenal glands during the development of deficiency. After a single injection of ACTH no substantial change was observed in the relative proportion of dehydroascorbic acid to ascorbic acid in the adrenal glands, although the concentration of ascorbic acid was seen to be temporarily depressed.

There was a remarkable increase in the weight of the liver in animals given ACTH; this was apparent after 2 days, and after 14 days amounted in young guinea-pigs to about 50 per cent. above the liver weight of control animals, and in adult guinea-pigs to an average of 39 per cent. During the first day or so the increase in the weight of the liver was due to extra glycogen and water, but thereafter there was an appreciable addition of protein. The size of the liver cells increased in proportion to the total increase in weight of the organ, as a result of an increased volume of the cytoplasm.

Administration of ACTH caused the percentage of fat in the liver to fall, but it had little effect on the concentration of sulphydryl compounds. The absolute amounts of water, glycogen, and protein continued to increase when the injections of ACTH were continued for periods up to 40 days, although there was some increase in the percentage of glycogen and some decrease in that of protein and fat, as compared with the controls. When administration of ACTH ceased the weight of the liver fell sharply, being about the same as that of control animals after 2 days, and about 10 per cent. lower than that of controls after 3 to 30 days. The glycogen content fell to within normal limits within 2 days and the protein content fell likewise some days later.

Cortisone had a similar but more intense effect on the liver of young guinea-pigs, but there was no significant change in the average weight of any other organ, except the kidneys, the weight of which increased from 8 to 20 per cent., according to the dose.

Similar effects were observed in rabbits, but not in young rats, mice, or chicks. *Robert de Mowbray.*

Effect of Prolonged Administration of Epinephrine on Adrenal Cortical Function and Epinephrine Tolerance in Chronic Asthmatics. LESLIE, A., BLAND, W. H., and ADAMS, W. S. (1953). *Lab. clin. Med.*, **41**, 865. 3 figs, 17 refs.

At the University of California Medical Center the opportunity was taken to investigate the effect of prolonged administration of adrenaline in five male patients who had been taking adrenaline regularly by subcutaneous injection for considerable periods for asthma the object being to determine whether there was any evidence of sustained adrenal stimulation of the hypothalamus-adrenal-pituitary system, or if after a time this

system became refractory. In addition, by giving regular doses of adrenaline for periods of one week interrupted by one week's treatment with pethidine ("Demeroj"), the question of adrenaline resistance and the possible restoration of sensitivity after deprivation was also studied. Lastly, the changes in the eosinophil count and in the sweat sodium content were studied during the administration of ACTH and compared with these values when adrenaline alone was given.

The authors found no evidence that adrenaline produced any long-standing stimulation of the pituitary-adrenal axis, or of any increased sensitivity to adrenaline after its discontinuation for a week. Even when the response to adrenaline was reduced the administration of ACTH still had a beneficial effect, indicating different modes of action of the two substances. There was not always a close correlation between clinical improvement with ACTH and the degree of eosinopenia or the reduction in the sweat sodium content. *K. Gurling.*

Surgery of the Adrenal Gland for Cushing's Syndrome. POUTASSE, E. F., and HIGGINS, C. C. (1953). *J. Urol.* (*Baltimore*), **70**, 129. 6 figs, 11 refs.

It is now generally accepted that all patients with Cushing's syndrome have hyperadrenocorticism, with excess of 11-oxysteroids. In some cases the condition is due to a tumour of the adrenal gland but more often to hyperfunction of the adrenal cortex, with or without hyperplasia. The stimulus causing the hyperadrenocorticism is not understood and it is only rarely that a basophilic pituitary tumour can be demonstrated. The excess of 11-oxysteroids produces the characteristic signs of Cushing's syndrome. If there is excess of steroid metabolites resembling androgens the androgenic syndrome and Cushing's syndrome may be found in the same individual. Cushing's syndrome is twice as common in women as in men. The average age of onset is 30, and the span of life is shortened, although occasionally spontaneous remission does occur.

In this paper the results of treatment of 28 cases of Cushing's syndrome are presented from the Cleveland Clinic, Ohio. Of these, two were found to have a malignant tumour of the adrenal cortex, four a benign solitary adenoma of the adrenal gland, two solitary benign adenomata in hyperplastic glands, and the remaining twenty no tumour. Methods of diagnosis are discussed. Treatment consists either of excision of any existing tumour or subtotal adrenalectomy in which all of one adrenal gland and 90 per cent. of the other is removed in a one-stage operation. At present it is not considered necessary to perform bilateral total adrenalectomy unless the disease is progressive following subtotal adrenalectomy and presents a threat to life. Simultaneous bilateral inspection of the adrenals is advised before any definitive operative procedure on the glands is performed. If both glands appear atrophic search must be made for a cortical adenoma in an aberrant situation, accessory adrenal tissue being present in 20 per cent. of all individuals.

The use of cortisone and other hormones in replacement therapy is discussed. Operation has been made safer by the preoperative administration of cortisone, which is continued in decreasing doses after operation, or it may have to be continued indefinitely if the remaining adrenal fragment is incompetent. ACTH may be used to stimulate an atrophic gland, and deoxycortone acetate (DOCA) may also be necessary after operation. With adequate resection of the adrenals almost all the abnormal features disappear, although osteoporosis, which is often present, is late in responding. Hypertension, possibly due to irreversible changes in the arteries, is sometimes uninfluenced by operation and serious vascular disease may occur at an early age in Cushing's syndrome in spite of adequate therapy.

In a group of eight patients operated on since cortisone became available there were no operation deaths. One died 9 months after operation from perforated duodenal ulcer, another required a second operation for total adrenalectomy, but the other six are well.

In an earlier group of twelve patients one died; in five undergoing bilateral hemi-adrenalectomy three are well, one is improved, and one died of adrenal failure.

Of five patients undergoing operative investigation only, three who were traced had all died of complications of Cushing's syndrome. *W. Skyrme Rees.*

Specific Water Diuresis Test for Adrenocortical Insufficiency. OLEESKY, S. (1953). *Lancet*, **1**, 769. 1 fig., 17 refs.

Among laboratory aids to the diagnosis of adrenocortical insufficiency Kepler's test is considered the most useful, but it is complicated and tedious to perform. Soffer and Gabrilove (*Metabolism*, 1952, **1**, 504) have proposed a simplified version of this test, but it is said to have the disadvantage that often the patient is unable to ingest the necessary quantity of water (1,500 ml.) without vomiting and that each of the two parts of the test lasts 5 hours. The present author now describes a modification of these tests which he claims is simpler to perform and more specific in its results.

Following overnight deprivation of fluid, the patient is asked to drink as much water as possible up to a total of 1 litre in 20 minutes. The urine flow is then measured at intervals of 15 to 20 minutes for 2½ hours. (The maximum rate of urine flow in adrenocortical insufficiency is low—less than 2 to 3 ml. per minute.) The test is repeated next day 4 hours after the oral administration of 50 to 75 mg. cortisone.

In performing this test it is necessary to observe the following precautions:

(1) the patient's serum sodium level must not be very low, because then even the administration of cortisone will fail to produce a normal diuresis;

(2) the dose of cortisone must not be less than 50 mg.;

(3) the control and test observations must be made at the same time of day;

(4) the water should be drunk when the cortisone activity is at its highest level as measured by eosinophil depression (4 to 8 hours after ingestion in adrenal insufficiency).

The author gives reasons for regarding this test as better than other excretory tests and discusses its use in differential diagnosis. *Norval Taylor.*

Enhancement of Adrenocorticotrophic Activity. COHEN, H., FREEDMAN, H. H., KLEINBERG, W., EISLER, M., and MARTIN, G. J. (1953). *Proc. Soc. exp. Biol.* (*N.Y.*), **82**, 749. 12 refs.

The authors present experimental evidence to show that the effect of a subcutaneous injection of ACTH (corticotrophin) on the adrenal cortex of the rat is enchanced by its administration in a medium which delays absorption of the hormone. Hypophysectomized Sprague-Dawley male rats of 110 to 115 g. body weight were used, each group being given a subcutaneous injection of 1 *U.S.P.* unit ACTH dissolved in 0·5 ml. of one of the following test solutions:

0·2 per cent. suramin,
5 per cent. phosphorylated hesperidin,
2·5 per cent. phosphorylated hesperidin,
5 per cent. hesperidin methyl chalcone,
15 per cent. gelatin,
15 per cent. gelatin plus 20 T.U. hyaluronidase,
15 per cent. gelatin plus 4 per cent. phosphorylated hesperidin.

Control animals received injections of the test solutions without ACTH. In each group the ascorbic acid content of the left adrenal gland was determined by the method of Mindlin and Butler 3 hours after the injection, and that of the right gland 6 hours after the injection, the effect of the ACTH being judged from the degree of depletion of adrenal ascorbic acid found.

Of the single agents tested, the most effective in enhancing the action of ACTH were phosphorylated hespiridin and heavy gelatin, while a combination of these two substances was even more effective, the maximum response being greater than with either agent alone and its appearance being delayed until the 6th hour. The possible mechanism of this delay of absorption was investigated *in vitro*, and the activity of phosphorylated hesperidin and hesperidin methyl chalcone in inhibiting the tryptic digestion of casein, as determined by the method of Anson (*J. gen. Physiol.*, 1938, **22**, 79), was shown to be similar in degree. It was therefore concluded that the delaying action of the former was due not to its antiproteolytic properties, but to its inhibiting effect on tissue hyaluronidase, the methyl chalcone of hesperidin having no such action. It is suggested, however, that the greater effectiveness of the combination of gelatin with phosphorylated hesperidin may be due to the antiproteolytic properties of the latter, the tissue proteinases being prevented from acting on the gelatin, which thus retains its depot effect for a longer period of time and reinforces the antihyaluronidase action of the phosphorylated hespiridin. *D. G. Adamson.*

Cortisone and the Metabolic Response to Injury. CAMPBELL, R. M., SHARP, G., BOYNE, A. W., and CUTHBERTSON, D. P. (1953). *Nature* (*Lond.*), **172**, 158. 1 fig., 21 refs.

It has been observed that the increased protein catabolism following injury such as fracture, strikingly resembles the effects of administration of adrenocorticotrophic hormone or cortisone. In the present investigation, carried out at the Rowett Research Institute, Aberdeen, the results in these two events were compared, using rats as the experimental subjects. Male rats weighing 300 g. and maintained on a constant food intake were divided into four groups of six animals each and treated in one of the following ways:

(1) subcutaneous implantation of 25 mg. cortisone acetate;
(2) fracture of the femur by open operation;
(3) subcutaneous implantation of 50 mg. cortisone acetate;
(4) fracture of femur plus implantation of 25 mg. cortisone acetate subcutaneously.

A control group was treated by sham operation and showed little disturbance of nitrogen metabolism.

Estimation of the urinary nitrogen output in the test animals showed that the effect of fracture was similar in character and magnitude to that of implanting a 25-mg. pellet of cortisone acetate. The result of adding a second 25-mg. pellet through the same incision was similar to that of simultaneous fracture and implantation of one pellet; in both cases the effect was greater than for one event only, but not as great as if they were additive. These observations suggest that the effect of fracture of the femur in the rat is roughly equivalent to the effect of the slow liberation of 25 mg. cortisone from the adrenal cortex, and that increasing the stimulus (as measured by cortisone) increases the response. It is not considered justifiable at present, however, to conclude from this that any such injury would cause the liberation of such a quantity of glucocorticoid from the adrenal cortex. *Nancy Gough.*

Postoperative Adrenal Cortical Insufficiency in Patients previously treated with Cortisone. SALASSA, R. M., BENNETT, W. A., KEATING, F. R., and SPRAGUE, R. G. (1953). *J. Amer. med. Ass.*, **152**, 1509. 5 figs.

In this paper from the Mayo Clinic two cases are described in which, after prolonged administration of cortisone for rheumatoid arthritis, the patients died from irreversible shock after a major surgical operation.

The first patient, a woman of 54 years, had received cortisone for one year before admission in a dosage of 75 mg. three times a week, increased after 4 months to 100 mg. a day. Symptoms of gastric ulceration developed and 7 days after admission a haematemesis occurred. A partial gastrectomy was performed, but the patient did not regain full consciousness; signs of shock developed and she died, despite emergency measures which included administration of 300 mg. cortisone.

The second patient, also a woman of 54 years, had received a prolonged course of both cortisone and ACTH for rheumatoid arthritis. During this treatment she developed moon-face. Administration of cortisone was discontinued when the patient was admitted to hospital for treatment of the rheumatoid arthritis, but intra-arterial injections of hydrocortisone to a total of 422 mg. were given in the 4½ months before bilateral bunionectomy was performed, the last injection being given 2 weeks before the operation. The patient withstood the operation well, but 15 hours afterwards shock developed which did not respond to cortisone and intravenous injection of hydrocortisone.

In both patients the basophilic cells of the anterior pituitary showed loss of granulation, vacuolization, and hyalinization, while the adrenal cortex was considerably decreased in thickness, owing to a diminished number of cells rather than to diminished cellular size. There was lack of lipoid material in the zona glomerulosa and zona fasciculata, with congestion of the zona reticularis.

The authors also examined the adrenal glands of adult patients who had died from various disease conditions for which they had received cortisone. It was found that there was often a decrease in the size of the glands, that though the total adrenal weight might be normal there could be quite marked histological changes, and that after cortisone has been discontinued for an interval of several weeks or more, signs of recovery were apparent. It is pointed out that these changes are secondary to depression of endogenous ACTH, and that the same situation, with the same hazards, might arise after prolonged treatment with this hormone.

In the authors' view, a patient who has received intensive ACTH or cortisone therapy with a period of 6 to 12 months before operation, particularly if there are signs of hypercorticism, should be regarded as having deficient reserve adrenocortical function. Intramuscular injections of 200 mg. cortisone should be given 48, 24, and 1 to 2 hours before operation, with a gradual tailing off of the drug during the subsequent 3 to 4 days. The patient should not receive intravenous infusion of glucose solution without sodium chloride, and morphine, which is also a special hazard in patients with deficient adrenocortical function, should be avoided.

G. A. Smart.

Effect of Colchicine on the Pituitary Gland and on the Adrenal Cortex. (Influenza della colchicina sull'ipofisi e sul corticosurrene.) LUCHERINI, T., SUMMA, C., and VOLPICELLI, M. (1953). *Poloclinico, Sez. med.*, **60**, 213. 56 figs, bibl.

The results are reported of a series of clinical and laboratory investigations which have been carried out at the Rheumatology Centre of the University of Rome into the antirheumatic activity of colchicine and the effect of the drug on pituitary and adrenocortical function. The chief findings were as follows:

Colchicine did not appear to increase the therapeutic action of cortisone in rheumatoid arthritis;

the improvement noted in ten patients who received 50 mg. cortisone intramuscularly and 1 to 2 mg. colchicine by mouth daily for 20 days showed no appreciable difference from that observed in ten comparable cases treated with cortisone only in the same dosage.

A single dose of 2 mg. colchicine by mouth to rheumatic subjects diminished the number of circulating eosinophils by an average of 13·2 per cent.

The same dose given daily increased the urinary excretion of 11-oxysteroids by an average of 39 per cent., suggesting that the drug has some adrenocorticotrophic effect.

In some experiments in animals it was found that colchicine reduced the spreading effect and suppressed some of the histological effects of hyaluronidase injected intradermally. After repeated administration of colchicine to guinea-pigs for 3 to 7 days, histological examination showed evidence of over-activity in the zona fasciculata and zona glomerulosa of the adrenal cortex, an increase in the eosinophil cells of the pituitary gland, and involution of lymphoid tissue, while after 10 days the liver showed vacuolization and glycogen infiltration, the appearances being similar to those found after the administration of cortisone. There were no changes in the pancreas, however, in contrast to the findings after cortisone administration. Colchicine was also shown to cause degenerative changes in the muscle fibres of the heart.

It is concluded that, despite its lack of short-term antirheumatic effect, colchicine has a definite ACTH-like action. Its clinical use over a long period is precluded by its toxic effects.

V. C. Medvei.

Further Studies on Blood and Bone Marrow after Administration of ACTH and Cortisone. [In English.] HÄVERMARK, N. G., and NORDENSON, N. G. (1953). *Acta haemat.* (*Basel*), **9**, 227. 4 figs, 16 refs.

In three patients suffering from arthritis, for which treatment with ACTH and cortisone was given at the Södersjukhuset, Stockholm, changes in the blood and bone marrow were observed. There was stimulation of erythropoiesis and of the formation of polymorphonuclear leucocytes, but not of lymphocytes. Treatment with ACTH, and to a lesser degree with cortisone, produced eosinopenia. The observations were not quite constant, and this the authors consider was due to the fact that the three patients received different dosages of the hormones. They are unable to say if the finding that cortisone had a less profound effect than ACTH on the bone marrow and peripheral blood picture was due to an essential difference between the action of the two drugs, or whether it was because ACTH was given in a higher dosage.

H. Lehmann.

Haematological Changes in the Bone Marrow and Peripheral Circulation due to Treatment with Cortisone and ACTH. (Modificazioni del quadro ematologico (midollare e periferico) in corso di cura con cortisone e ACTH.) SCALABRINO, R., CURTARELLI, G., and BOMBELLI, R. (1952). *Haematologica*, **36**, 823. 16 figs, bibl.

At a Milan hospital careful serial examinations of the blood picture were made on a series of 32 patients with a variety of acute, subacute, and chronic rheumatic conditions, including a number with carditis, and certain other diseases, all of whom were treated with cortisone or ACTH for variable periods and with a variable dosage.

In nineteen patients the total leucocyte count increased and in eleven it decreased. The lymphocyte count decreased in the majority of patients, although this decrease was not constant and did not always persist, and in the spleen and lymph nodes the lymphoid centres became less marked and less cellular when the hormones were given in large doses. The neutrophil granulocyte count increased in almost all cases, and that of eosinophil granulocytes decreased in most, but only temporarily.

In the bone marrow the number of eosinophil cells showed no changes with treatment. A slight rise in the reticulocyte count occurred in eleven patients, and the haemoglobin content and erythrocyte count increased slightly—partly as a result of treatment, but possibly owing to a natural remission of the disease process in some cases.

E. Neumark.

Effect of Cortisone and ACTH on the Phagocytic Activities of Leucocytes and Macrophages. (Untersuchungen über den Einfluss von Cortison und ACTH auf die Phagozytose der Leukozyten und Makrophagen.) MOESCHLIN, S., ZURUKZOGLU, W., and CRABBE, J. (1953). *Acta haemat.* (*Basel*), **9**, 277. 3 refs.

At the University of Zürich the effect of ACTH (corticotrophin) and cortisone on the phagocytic activity of the leucocytes and the macrophages of rabbits was investigated.

Macrophages were obtained from a pleural exudate induced by the intrapleural injection of broth and gum arabic; the exudate was mixed with suspensions of *Staphylococcus aureus* and the number of cells containing ingested bacteria estimated after 30 minutes. ACTH or cortisone added *in vitro* had no effect on phagocytosis, but when either drug had been given to the animals for a week or more before the experiment there was slight but distinct inhibition, becoming more marked as the period of administration was increased. This result is attributed to a reduction in the production of macrophages and in the potency of chemotactic factors. In the blood of animals treated with cortisone, however, no inhibition of phagocytosis by the leucocytes could be demonstrated.

E. Neumark.

Thymus Involution Test for ACTH. [In English.] THING, E. (1953). *Acta endocr.* (*Kbh.*), **13**, 343. 4 figs, 7 refs.

The usual method used for the assay of ACTH (corticotrophin), the ascorbic acid depletion test, suffers from the disadvantage that it requires hypophysectomized animals. A method involving the use of intact animals, based on an observation by Hayashida and Li (*Endocrinology*, 1952, **50**, 187) that the weight of the thymus decreases under the influence of ACTH in normal 21-day-old rats, has been described by Bruce and others (*Lancet*, 1952, **1**, 790), and has been further investigated by the present author, 1,500 nestling rats 7 to 10 days old being used. Since the thymus requires a constant stimulus, the ACTH was administered in an oily medium consisting of arachis oil with 5 per cent. beeswax. Injections were given once daily for 3 days, and 24 hours later the thymus was removed and weighed. From the average results obtained with different doses, dose-response curves were constructed. The oily medium alone was without effect on the thymus, and stress substances such as formalin had to be administered in very large amounts before more than slight involution occurred, whereas it was confirmed that a quantitative relation existed between the dose of ACTH administered and the degree of thymus involution produced. The reliability of the tests seemed to be equal to that of established methods, but its sensitivity was less, the amount of active material necessary to produce a significant response being about ten times greater than in the ascorbic acid depletion test.

Nancy Gough.

Enhancement of the Effect of ACTH on the Adrenal Weight and the Thymus Involution in Hypophysectomized Rats when administered in Beeswax-Oil. [In English.] THING, E. (1953). *Acta endocr.* (*Kbh.*), **13**, 353. 2 figs, 12 refs.

ACTH (corticotrophin) in oil-beeswax suspension was administered to adult hypophysectomized rats to investigate its ability to produce adrenal hypertrophy and thymus involution. The study was begun 14 days after hypophysectomy and the 155 rats were divided into three groups, the first being given ACTH in aqueous solution, and the second ACTH in arachis oil with 5 per cent. beeswax, the third being used as controls. The ACTH was given at various dosage levels (five animals per dose), the doses given in aqueous solution being ten times greater than those given in oily suspension. The degrees of thymus involution and adrenal hypertrophy found after 3 days' treatment were about equal in both groups, indicating that one dose of the slowly-absorbed ACTH preparation is equal in effect to ten doses of aqueous ACTH. Nevertheless, the amount of hormone required to obtain a measurable response was ten times greater than that required when intact nestling rats were used, and the author therefore concludes that the method of assay of ACTH by determination of its effect on the adrenal weight and thymus involution in adult hypophysectomized rats is of no practical value.

Nancy Gough.

Correlation of the Eosinophil Count with the Clinical Course during Cortisone and ACTH Therapy. MARTIN, J. R., and PATTEE, C. J. (1953). *Canad. med. Ass. J.*, **68**, 565. 25 refs.

The relationship, if any, between a rise or fall in the eosinophil count and the clinical changes in patients receiving cortisone or ACTH was studied at Queen Mary Veterans' Hospital, Montreal. In 35 of 56 patients, most of whom were suffering from bronchial asthma or rheumatoid arthritis, there was a fall in the eosinophil count of at least 50 per cent. after administration of cortisone, but no parallel was observed between this fall and the efficacy of the treatment. In twenty of these 35 patients the eosinophil count rose later during treatment ("escape" of the eosinophils), but once again this did not parallel an improvement or deterioration in the clinical condition. In the authors' view ACTH is a stronger eosinopenic agent than cortisone [this view, however, is based on the results in only two cases, in which a course of ACTH was given after a course of cortisone.] They state that if two courses of cortisone are given the fall in the eosinophil count is less during the second course [but this finding is based on three cases only, in one of which the second course was given after an interval of one year]. The authors found wide variations in the eosinophil count in the same patient, even when it was determined at the same time each day. [These variations, which have been noted by many other workers, do not

prevent them from forming theories based on this wide scatter.] *H. Herxheimer.*

Oral Cortisone in the Treatment of Hay Fever. SCHILLER, I. W., and LOWELL, F. C. (1953). *J. Allergy*, **24**, 297. 9 refs.

A series of 51 patients with hay-fever (caused in most cases by ragweed and in others by grass pollen) who had been unsuccessfully treated by other methods received 100 mg. cortisone daily by mouth in divided doses for 4 days. In 42 instances complete or satisfactory relief was obtained, mostly on the 1st or 2nd day of treatment. Relapse occurred between the 1st and 7th days after stopping the treatment in twenty cases. In the remainder the symptoms did not return although the pollen season continued. *H. Herxheimer.*

Cortisone in Ocular Allergy. A Study of its Mode of Action. [In Japanese.] MIZUKAWA, T., TAKAGI, Y., SUZUE, T., and KISHIMOTO, S. (1953). *Acta Soc. ophthal. jap.*, **57**, 1067. 7 figs, 8 refs.

Rabbits sensitized with cattle serum were given anterior chamber injections of the serum. The protein content of aqueous, blood eosinophils, ascorbic acid (reduced form) in ocular tissues, cholinesterase activity in choroid, and fraction of serum protein were then measured. *Y. Mitsui.*

Bilateral Acute Neuroretinitis with Sarcoidosis treated with Corticotropin and Cortisone. FINE, M. (1953). *Arch. Ophthal.* (*Chicago*), **50**, 358. 3 figs.

A case of sarcoidosis (lymph gland biopsy) with bilateral anterior uveitis of mild degree, and fairly severe acute neuro-retinitis, responded very quickly to oral cortisone and intravenous corticotropin. The central and paracentral scotomata, which were the main symptom, rapidly cleared; no report on the lymphatic condition is given. *J. E. M. Ayoub.*

Effect of Cortisone on the Activity of Iridocyclitis complicating Rheumatoid Spondylitis. WILSON, W. M. G., BAGNALL, A. W., and MCINTOSH, H. W. (1952). *Treat. Serv. Bull.*, **7**, 321.

Bilateral cataract extractions were performed on a patient with bilateral iridocyclitis and rheumatoid spondylitis. The patient received 100-300 mg. cortisone intramuscularly daily, for 45 days before operation, and this medication was continued after operation. Despite this treatment a cyclitic membrane formed in the pupillary area about 3 weeks post-operatively. *C. McCulloch.*

Intravenous Corticotropin in Angioneurotic Oedema of the Orbit. CALLAHAN, A. (1953). *Arch. Ophthal.* (*Chicago*), **50**, 286. 1 fig., 3 refs.

A case of severe angioneurotic oedema of the orbit, which had recurred six times in 7 years, was successfully treated with intravenous corticotropin. *S. J. H. Miller.*

Value of Adrenocorticotropic Hormone in Herpes Zoster Ophthalmicus. POULIN, J. E. (1952). *J. Maine med. Ass.*, **43**, 301. 4 refs.

Effects of ACTH in a Case of Primary Malignant Basedowian Exophthalmos. (Effets de l'ACTH dans un cas d'exophtalmie basedowienne maligne primitive.) DECOURT, J., DOLLFUS, M. A., DUBOIS-POULSEN, A., and CAMBIER, J. (1952). *Ann. endocr.* (*Paris*), **13**, 164.

Cortisone and ACTH in Eye Diseases. SOBHY, M. (1952). *J. Egypt. med. Ass.*, **35**, 794.

Retrobulbar Optic Neuritis treated with Cortisone. (Reporte de un caso de neuritis optica retrobulbar, tratado con cortisona.) RAMIREZ GILBON, J. (1952). *Bol. Hosp. oftal. Mex.*, **5**, 183.

Sjögren's Syndrome treated with Cortisone. (Un caso de síndrome de Sjögren, tratado con cortisona.) FERNÁNDEZ Y FERNÁNDEZ, M., and MARANON, G. (1952). *Gac. méd. esp.*, **26**, 199.

Laboratory Examinations as a Guide to the Institution and Management of Pituitary and Adrenocortical Hormone Therapy in Rheumatology. (Renseignements fournis par les examens humoro-biologiques pour l'institution et la conduite de l'hormonothérapie hypophyso-cortico-surrénale en rhumatologie.) CHEVALLIER, J. (1953). *Presse therm. clim.*, **90**, 165. 12 refs.

Indications and Contraindications for Adrenocortical Hormone Therapy in Rheumatology. (Indications et contre-indications de la corticothérapie surrénale en rhumatologie.) BOUREL, M. (1953). *Presse therm. clim.*, **90**, 149.

Treatment of Joint Disease with Intra-Articular Hydrocortisone. (Om behandling af ledlidelser med hydrocortison intraarticulaert.) HENRIKSEN, E., and NYFOS, L. (1953). *Ugeskr. Laeg.*, **115**, 1763. 2 figs, 18 refs.

Hydrocortisone and Hydrocortisone Acetate in Rheumatology. (Hydrocortisone et acétate d'hydrocortisone en rhumatologie.) FRANÇON, J. (1953). *Presse therm. clim.*, **90**, 170.

Prolonged Cortisone Therapy. (Les cures prolongees de cortisone.) BICKEL, G. (1953). *Schweiz. med. Wschr.*, **83**, 1151. 35 refs.

Action of Cortisone on Polyarthritis in the Rat. (Die Wirkung von Cortison auf die Polyarthritis der Ratte.) SIEBENMANN, R., and UEHLINGER, E. (1953). *Z. Rheumaforsch.*, **12**, 217. 4 figs, 27 refs.

Other General Subjects

Dupuytren: an Undeserved Reputation. (Dupuytren: una fama immeritata.) FRANCESCHINI, P. (1953). *Riv. Storia Sci. med. nat.*, **44**, 92. 7 refs.

In this iconoclastic essay the author examines the career of Baron Dupuytren and concludes that historians have continued to accept this "celebrated" French surgeon at his own valuation without real justification.

The many faults in his personal character have long been admitted; in addition, the author cites the numerous achievements of Dupuytren's contemporaries in one of the most brilliant periods of French medicine and shows how Dupuytren, through ignorance or jealousy, did his best to minimize or deny their importance. The most striking examples of this harmful egomania are his treatment of Louyer-Villermay's account of appendicitis (1824), owing to which it is still not appreciated that this work anticipated that of Fitz; and—more important—the extraordinary history of "Lembert's suture". The author states that this epoch-making advance in intestinal surgery was really carried out by Charles Lambert, a pupil of Dupuytren's hated rival, Lisfranc, and was reported to the Académie Royale de Médecine on January 26 1826. Dupuytren later attributed it to his own pupil, Antoine Lembert, and said that even Lembert had been anticipated by another of his pupils, Jobert de Lamballe ("both are equally perfect"). In fact, the latter had merely repeated methods used in the 17th and 18th centuries by Palfyn and Ledran and had taken them no farther. [Those who wish to investigate this claim are referred to the author's history of intestinal suture (*Rassegna Clinico-Scientifica*, 1947, **23**, 84).]

[Without accepting all the author's conclusions, it must be admitted that he has presented a strong case for a critical reassessment of Dupuytren's role in the history of surgery.] *F. N. L. Poynter.*

Adrenaline Cream. An Assessment of its Value in the Rheumatic Disorders. LAWRENCE, J. S., SLADDEN, R. J. (1953). *Brit. med. J.*, **1**, 1085. 4 refs.

The authors review the somewhat contradictory literature on the results achieved by massage with a cream containing adrenaline in the treatment of patients suffering from rheumatic conditions. Their own trial at the Walkden Miners' Clinic and Rheumatism Research Centre, Manchester University, embraced investigation both of the efficiency of adrenaline cream as a pain-reliever and of the recovery times of patients under treatment. In one investigation 65 patients were treated, approximately one-half of them with adrenaline cream and one-half with a similar cream containing no adrenaline. At the time of treatment neither the doctors nor the physiotherapists knew which cream they were using. In another investigation sixty patients were treated with adrenaline cream, by dry massage, and without massage for three consecutive periods, but the order in which the treatments was carried out varied, and other physiotherapeutic measures, such as heat treatment, were applied without interruption. Results were assessed on the basis of whether relief from pain was complete, partial, or non-existent. It was found that dry massage gave more relief than massage with simple cream, and that massage with adrenaline cream "produced complete relief in a significantly greater proportion of patients than simple cream". It was concluded that massage with adrenaline cream and dry massage produced a similar degree of palliation.

Another investigation was carried out to ascertain the effect of adrenaline cream on recovery, 64 alternate patients being treated with either adrenaline cream or simple cream until complete relief was obtained or no further improvement could be expected. While the final results achieved in the two groups were the same, it was found that there was a significant difference in the time taken to return to work between the two groups: all those in the group treated with simple cream returned to work by the end of the investigation, but of those treated with adrenaline cream three failed to return to work and two who were originally at work had to stop.

Discussing their findings, the authors point out that the mode of action of adrenaline cream is by no means clear, but they suggest that the delay in recovery following the use of this substance may be due to an interference with the pain-defence mechanism. *W. Tegner.*

Children's Eyes and Rheumatism. [In Russian.] PAVLOV, N. M., and MOLCHANOVA, L. A. (1953). *Vestn. oftal.*, **32**, 14. 8 refs.

The blind spot may be enlarged in the vertical meridian and so point to changes in the blood vessels of the optic nerve. As part of the affection of the vascular system, the retinal vessels may be involved, producing a concentric narrowing of the field of vision. It is possible that some hardly noticeable scleritis, especially on the posterior segment of the eyeball, may lead to myopia. The nutrition of the sclera may be affected. *N. Pines.*

Classification of the Rheumatic Diseases. (Sistemica delle malattie reumatiche.) LUCHERINI, T. (1953). *Policlinico, Sez. prat.*, **60**, 1333. 2 figs, 17 refs.

Sex Hormones in Rheumatology. (Les hormones génitales en rhumatologie.) DURUPT, L. (1953). *Presse therm. clim.*, **90**, 157.

Unfamiliar Rheumatic Syndrome. (Ein bisher wenig beachtetes rheumatisches Syndrom.) SCHLIEPHAKE, E., and BUTKA, K. (1953). *Z. Rheumaforsch.*, **12**, 303. 2 refs.

Corticotherapy and Spa Treatment in Rheumatism. (Corticothérapie et cures hydrominérales des rhumatismes.) FRANÇON, F. (1953). *Presse therm. clim.*, **90**, 161. 2 refs.

Rheumatism and the Appendicular Syndrome. (Reumatismo y sindrome apendicular.) MANZANARES, E., and GRICHENER, A. (1953). *Rev. argent. Reum.*, **18**, 113. 32 refs.

Leukergy in Diseases of the Locomotor Apparatus. (La leuchergia in alcune malattie dell'apparato locomotore.) DANEO, V., and SECONDO, G. (1953). *Reumatismo*, **5**, 313. 27 refs.

Dental Focal Sepsis and Clinical Rheumatism. (El foco septico dentario desde el punto de vista de la clinica reumatologica.) COSTA BERTANI, G. (1953). *Rev. argent. Reum.*, **18**, 131. 9 refs.